1268243

PATENT SPECIFICATION

(11) 1 268 243

NO DRAWINGS

(21) Application No. 12844/69 (22) Filed 11 March 1969

(31) Convention Application No. 711 897 (32) Filed 11 March 1968 in

(33) United States of America (US)

(45) Complete Specification published 22 March 1972

(51) International Classification C 07 d 41/00; A 61 k 27/00

(52) Index at acceptance

C2C 179—271—281 1E4K3 1E4K6 213 220 227 22Y 246
247 250 251 25Y 290 29X 29Y 305 30Y 314 31Y
321 322 323 326 32Y 332 337 342 34Y 351 352
355 360 362 364 365 366 367 36Y 385 396
3A10E3D4 3A12A4A 3A12A4B 3A12B3 3A12B7
3A12C3 3A12C5 3A12C6 3A13B3 3A13C10D
3A13C10F 3A13C10H 3A13C1B 3A13C1C 3A13C6A 3A13C9 3A13D 3A7V1G2

PATENTS ACT 1949

SPECIFICATION NO 1268243

In pursuance of Section 8 of the Patents Act 1949, and of a correction under Section 76 the Specification has been amended in the following manner:-

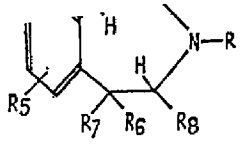
Page 2, line 17, *delete* methoxy. *insert* methyl; provided that at least one of R, R^3, R^4, R^5, R^6, R^7, or R^8 is other than hydrogen when R1 is hydrogen and R^3 is phenyl; provided that at least one of R^2, R^3 or R^8 is other than hydrogen when R is hydrogen, alkyl, alkenyl, or aralkyl and R1 is hydrogen or alkyl, and R^4 and/or R^5 is independently hydrogen, alkyl, alkoxy, hydroxy or halogen and R^6 is hydrogen or alkyl and R^7 is phenyl

Page 40, line 10, *after* methyl *insert* provided that at least one of R, R^3, R^4, R^5, R^6, R^7, or R^8 is other than hydrogen when R1 is hydrogen and R^3 is phenyl; provided that at least one of R^2, R^3 or R^8 is other than hydrogen when R is hydrogen, alkyl, alkenyl, or aralkyl and R1 is hydrogen or alkyl, and R^4 and/or R^5 is independently hydrogen, alkyl, alkoxy, hydroxy or halogen and R^6 is hydrogen or alkyl and R^7 is phenyl

R 1531

THE PATENT OFFICE
22 December 1972

Formula I



or the pharmaceutically acceptable addition salts thereof, wherein R is H, lower alkyl; dialkylamino-alkyl, lower alkenyl containing 3—6 carbon atoms: aryl-C_3—C_6 alkenyl; cycloalkyl-alkyl, for example 2-(1-adamantyl)-ethyl-(adamantyl moiety unsubstituted or substituted with NH_2, OH, OCH_3, halogen, alkyl); aryl-cycloalkyl-alkyl, propargyl; aryl-lower alkyl, the aryl group selected from phenyl, tolyl, nitrophenyl aminophenyl, acylaminophenyl, methoxyphenyl, hydroxyphenyl, methylaminophenyl, ethylamino-phenyl, or dimethylaminophenyl; a lower alkyl ester of hydroxyalkyl: a heterocyclic group, an alkyl group substituted by a heterocyclic ring (unsubstituted or substituted with one or more phenyl, hydroxyl or acyl groups), 2-phthalimidoethyl-(the phenyl moiety unsubstituted of substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-(2-isoindolinyl)-ethyl-(the phenyl moiety unsubstituted or

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C2C 179—271—281 1E4K3 1E4K6 213 220 227 22Y 246 247 250 251 25Y 290 29X 29Y 305 30Y 314 31Y 321 322 323 326 32Y 332 337 342 34Y 351 352 355 360 362 364 365 366 367 36Y 385 396 3A10E3D4 3A12A4A 3A12A4B 3A12B3 3A12B7 3A12C3 3A12C5 3A12C6 3A13B3 3A13C10D 3A13C10F 3A13C10H 3A13C1B 3A13C1C 3A13C4C 3A13C6A 3A13C9 3A13D 3A7V1A4 3A7V1E1 3A7V1G2 3A7V1J1 3A7V2A4 3A7V2E1 3A7V2G2 3A7V2J1 3A7V2K3B 3A7V3A2 3A7V3F1 3A7V3J5 3A8A4 3A8B2 3A8C3 3A8G1 3A8K 43X 45X 45Y 509 50Y 510 51X 534 601 610 613 615 620 621 623 624 625 62X 650 656 660 661 662 670 672 675 680 681 682 699 760 775 776 790 79Y KP LF LH LM MB MM NJ QL QS SG ZH

(54) 1,2,4,5-TETRAHYDRO-3H,3-BENZAZEPINES

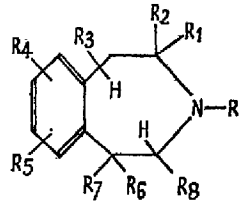
(71) We, WALLACE & TIERNAN INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 91 South Harrison Street, City of East Orange, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to substituted 1,2,4,5-tetrahydro-3H,3-benzazepines.

The compounds of this invention are useful as agents for producing analgesia and thus relieving pain in animals. They are also useful as antagonists of narcotics such as morphine.

As used throughout the following description and claims, the term "lower" means a group containing from 1 to 5 carbon atoms.

According to the present invention there is provided a compound of the formula:



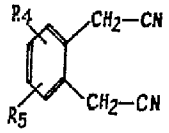
Formula I

or the pharmaceutically acceptable addition salts thereof, wherein R is H, lower alkyl; dialkylamino-alkyl, lower alkenyl containing 3—6 carbon atoms: aryl-C_3—C_6 alkenyl; cycloalkyl-alkyl, for example 2-(1-adamantyl)-ethyl-(adamantyl moiety unsubstituted or substituted with NH_2, OH, OCH_3, halogen, alkyl); aryl-cycloalkyl-alkyl, propargyl; aryl-lower alkyl, the aryl group selected from phenyl, tolyl, nitrophenyl aminophenyl, acylaminophenyl, methoxyphenyl, hydroxyphenyl, methylaminophenyl, ethylaminophenyl, or dimethylaminophenyl; a lower alkyl ester of hydroxyalkyl: a heterocyclic group, an alkyl group substituted by a heterocyclic ring (unsubstituted or substituted with one or more phenyl, hydroxyl or acyl groups), 2-phthalimidoethyl-(the phenyl moiety unsubstituted of substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-(2-isoindolinyl)-ethyl-(the phenyl moiety unsubstituted or

SEE CORRECTION SLIP ATTACHED

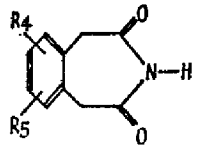
substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-benzyl-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o, m, or p*-position with NH_2, OH, OCH_3); 2-(4-phenyl-1-piperazinyl)-ethyl-(the phenyl moiety unsubstituted or substituted in the *o, m, p*-position with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-(*o*-methylbenzyl)-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o, m,* or *p*-position with NH_2, OH, OCH_3, halogen, alkyl): R^1 is hydrogen and R^2 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl, or R^1 and R^2 are lower alkyl; R^3 is hydrogen or lower alkyl; R^4 and R^5 are hydrogen, lower alkoxy, CH_3OCH_2O—, hydroxy, pyridine carboxylic acid ester of hydroxy group, amino, lower alkyl, halogen or nitro; R^6 and R^7 are hydrogen, lower alkyl, phenyl or phenylalkyl; R^8 is hydrogen, lower alkyl, phenyl or phenylalkyl; provided that when R^1, R^2, R^3, R^5, R^6, R^7, and R^8 are hydrogen and R is allyl, dialkylaminoalkyl or unsubstituted heterocyclyl-alkyl, R^4 is hydroxyl; provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 is other than hydrogen when R is either hydrogen, lower alkyl, allyl or phenyl-lower alkyl; and that neither R^4 nor R^5 is 6-chloro when R, R^1, R^2, R^3, R^6, R^7, and R^8 are hydrogen and provided that when R^4 and R^5 are methoxy, R is not hydrogen or methoxy.

In the following discussion of the process of the invention the symbols R through R^8 are to be regarded as defined as above unless there is a specific indication to the contrary in the discussion. The compounds of the invention wherein R is hydrogen may be prepared by treating a compound of the formula



Formula II

with a hydrogen halide in a polar solvent such as acetic acid, warming the resulting 2-amino-4-halobenzazepine with water to provide a cyclic imide of the formula



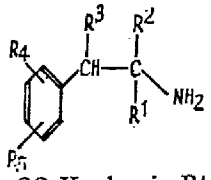
Formula III

and selectively reducing the carbonyl groups adjacent the imido group in the compound of Formula III.

Borane is a suitable reagent for use in reducing the carbonyl groups of the compound of Formula III.

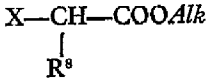
The compounds of the invention wherein R is hydrogen may also be prepared by hydrogenating a compound of Formula II. The hydrogenation is preferably effected catalytically using Raney nickel catalyst.

The compounds of the invention wherein R is hydrogen and any of the substituents R^1 through R^7 are lower alkyl, phenyl or phenyl lower alkyl may be prepared by reacting an amine of the formula



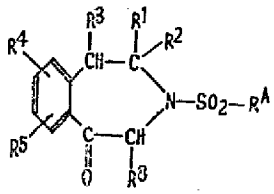
Formula IV

with a compound of the formula R^A—SO_2X wherein R^A is an organic radical and X is halogen, reacting the corresponding sulfonamide thus obtained with an ester of the formula



Formula V

wherein *Alk* is a hydrocarbon group and X is halogen, hydrolyzing the resulting ester, treating the acid thus obtained with a halogenating agent such as sulfonyl chloride to provide the corresponding acid halide, adding the acid halide to a cold suspension of aluminum trihalide to provide a benzazepinone of the formula



Formula VI

selectively reducing the carbonyl group in the azepinone moiety of the compound of Formula VI and splitting off the radical $R^A—SO_2—$ therefrom.

p-Toluenesulfonyl chloride is prepared for use as the compound of the formula $R^A—SO_2X$ while ethylbromoacetate or appropriately substituted derivative thereof is preferred as the ester of Formula V.

Sodium borohydride is a preferred reagent for use in reducing selectively the carbonyl group in the compound of Formula VI.

The compounds of Formula I wherein R is other than hydrogen may be prepared by reacting such a compound in which R is hydrogen with a reagent which will replace the hydrogen with one of groups R other than hydrogen. Such reagents include compounds of the formulas RX and R—C: OX wherein R is other than hydrogen and X is halogen, as well as aldehydes and ketones having at least three carbon atoms.

When a reagent of formula R—C: OX is used the carbonyl moiety is subsequently selective reduced to a methylene group. Lithium aluminum hydride is a preferred reagent for the reduction.

When an aldehyde of ketone is used as the reagent the double bond in the moiety attached to the nitrogen atom in the azepine ring of the product may be reduced. Sodium borohydride is preferred for the reduction.

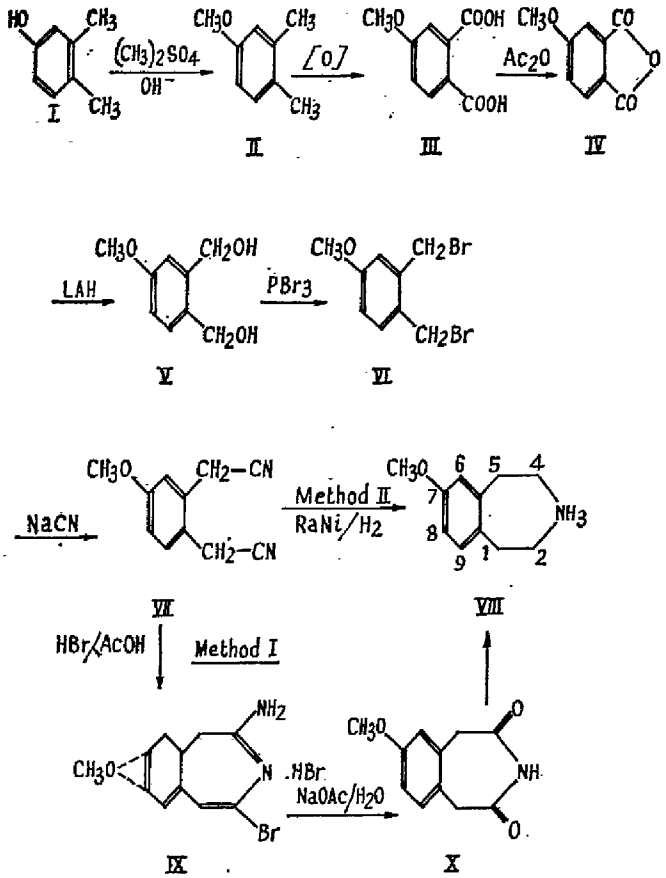
Suitable changes can be made in the substituents R^4 and R^5 in compounds of Formula I by means apparent to those skilled in the art. In one embodiment of the process of the invention, compounds of Formula I wherein R is hydrogen and at least one of R^4 and R^5 is an alkoxy group, are treated with aqueous hydrogen halide, preferably the bromide, to cleave the alkoxy group and provide a corresponding hydroxy group. The cleavage may be effected before or after the reaction of the compound of Formula I with compounds of formulas RX and RC: OX or an aldehyde or a ketone as discussed above.

Being organic bases the above compounds readily form salts with organic or inorganic acids such as hydrochloric, maleic, tartaric, sulfuric, and other nontoxic acids to form pharmaceutically acceptable acid addition salts.

Particularly satisfactory compounds from the point of view of analgesia and narcotic antagonism are compounds in which R^4 and R^5 are hydroxy or lower alkoxy.

The following Reaction Scheme A illustrates graphically two general techniques for preparing a representative compound of Formula I wherein R is a hydrogen atom, one of R^4 and R^5 is a methoxy group and the other a hydrogen atom, substituents R^1 to R^3 and R^6 to R^8 being hydrogen.

REACTION SCHEME A
Preparation of 7-Methoxy-1,2,4,5-Tetrahydro-3H,3-Benzazepine



The following procedures illustrate the preparation of intermediates used in the synthesis shown in the preceding reaction scheme.

Procedure I

3,4-Dimethyl anisole

3,4-Dimethylphenol (1 kg., 8.2 m) was suspended in water (3,300 ml.) and the stirred mixture was warmed to 45°C. The heat source was removed. With constant stirring, dimethyl sulfate (1,310 gm., 10.4 m) and a solution of sodium hydroxide (576 gm., 14.4) in water (1,480 ml.) were added in alternate portions so that the heat of reaction maintained the temperature at 47—50°C. The addition took about 5 hours. The resulting mixture was stirred at room temperature for a further 3 hours and then it was allowed to stand overnight at room temperature.

The reaction mixture was extracted with chloroform 1×800 ml., 3×400ml.). The combined chloroform layers were washed with water (3×200 ml.). After drying the chloroform solution over anhydrous magnesium sulfate, the solvent was evaporated on a rotatory evaporator at 15 mm. The light yellow oil which remained was distilled at 7 mm pressure and the fraction boiling at 85—88° was collected. wt.=942 gm.

Procedure II

4-Methoxyphthalic acid

3,4-Dimethylanisole (250 gm., 1.84 m) was suspended in water (7 *l.*) at 70°C. Potassium permanganate (2 kg., 12.6 m) was added portionwise at a rate which maintained the temperature between 75—85°C. The addition was complete in 5 hours. The reaction mixture was stirred a further 3 hours, without heating and then it was allowed to stand overnight at room temperature. The precipitated manganese dioxide was removed by suction filtration. Sodium chloride (1,500 gm.) was added to the filtrate which was then acidified with conc. hydrochloric acid to pH 1—2 (approx. 800 ml.). The precipitated solid was extracted into ethyl acetate (3×1*l.*). The ethyl

acetate extract was dried over anhydrous magnesium sulfate and then the solvent was evaporated at 15 mm. The residual solid had m.p. 168—174°. wt.=240 gm.

Procedure III

4-Methoxyphthalic anhydride

4-Methoxyphthalic acid (959 gm., 5.06 m) and acetic anhydride (2 *l.*) were mixed together and warmed to reflux. After 2 hours at reflux the solution was filtered while hot. The filtrate was cooled to room temperature and then it was cooled at —70°C. overnight. The solid precipitate was recovered by suction filtration, washed with petroleum ether (40—60°) and air dried. wt.=649 gm., m.p. 89—94°C.

The acetic anhydride mother liquors were evaporated to dryness at 15 mm. The residue was dissolved in ethyl acetate (1 *l.*) and the solution was washed with water (2×500 ml.) saturated sodium carbonate solution (2×500 ml.), water (500 ml.) and saturated saline solution (500 ml.). The ethyl acetate was dried over anhydrous magnesium sulfate and evaporated at 15 mm. The solid obtained had m.p. 89—93°. wt.=103 gm.

Procedure IV

4-Methoxy-o-xylenol

Lithium aluminum hydride (75 gm., 1.98 m) was suspended in tetrahydrofuran (2 *l.*) in an atmosphere of nitrogen at room temperature. To the stirred suspension was added dropwise a solution of 4-methoxyphthalic anhydride (250 gm., 1.40 m) in tetrahydrofuran (500 ml.) during 3 hours. The resulting reaction mixture was warmed to reflux for 2 hours and then it was allowed to stand at room temperature overnight. Water (75 ml.), 15% sodium hydroxide solution (75 ml.) and water (225 ml.) were added successively to the stirred, ice-cooled reaction mixture. Stirring was continued for a further hour, then the salts were filtered off. The filtrate was dried over magnesium sulfate. The dried solvent was evaporated at 15 mm. A colorless oil was obtained which solidified on standing to give the diol. m.p. 69—73°C. wt.=217 gm. b.p. 146°C/.025 mm.

Anal. Calc. for $C_9H_{12}O_3$: C, 64.27; H, 7.19.
Found: C, 64.01; H, 7.43.

Procedure V

4-Methoxy-α,α'-dibromo-o-xylene

4-Methoxy-o-xylenol (250 gm., 1.49 m) was suspended in dichloromethane (2.5 *l.*) at room temperature. Phosphorous tribromide (417 gm., 1.49 m) was added dropwise during 5½ hours. The temperature never exceeded 35°C. The first 100 ml. of bromide was added in 5 hours, and the remainder in 30 minutes. The reaction mixture was stirred for a further 2 hours then it was cooled to 10° and water (500 ml.) was added in 10 minutes. The temperature remained below 25°. After a further 5 minutes the dichloromethane was separated and washed with saturated sodium carbonate solution (500 ml.), water (2×400 ml.) and saturated brine solution (400 ml.). The dichloromethane solution was dried over magnesium sulfate. Evaporation of the solvent at 15 mm pressure afforded a solid m.p. 48—50°. wt.=430 gm.

The product was recrystallized from petroleum ether (40—60°). m.p. 49—49.5°.

Anal. Calc. for $C_9H_{10}Br_2O$: C, 37.04; H, 3.43, Br, 54.36.
Found: C, 37.15; H, 3.60; Br, 54.42.

Procedure VI

4-Methoxy-o-phenylenediacetonitrile

Finely ground sodium cyanide (73 gm., 1.48 m) was suspended in dimethylsulfoxide (500 ml.) by means of a "Vibro-Mixer". A solution of 4-Methoxy-α,α'-dibromo-o-xylene (113 gm., 0.384 m) in dimethylsulfoxide (200 ml.) was added dropwise to the cyanide suspension. The internal temperature was kept at 35—38°C. by means of an ice bath. The addition took 15 minutes. Agitation of the reaction mixture was continued for a further 1½ hours. The reaction mixture was poured into water (4 *l.*). The aqueous mixture was extracted with ether (2×1 *l.*, 3×500 ml.) and the combined ether extracts were washed with dilute hydrochloric acid (6N) (2×500 ml.), saturated sodium carbonate solution (1×500 ml.), water (3×500 ml.) and saturated sodium chloride solution (2×500 ml.). The ether layer was dried over magnesium sulfate. The dried ethereal solution was evaporated to an oil which was

distilled and the fraction with boiling range 160—165° (.1 mm) was collected. wt.=53 gm. The oil obtained was crystallized from ether (650 ml.) to give 45 gm. (m.p. 51—53°). A second crop of 5.8 gm. (m.p. 49—51°) was obtained.

Anal. Calc. for $C_{11}H_{10}N_2O$: C, 70.78; H, 5.48; N, 14.90.
Found: C, 70.95; H, 5.41; N, 15.05.

Procedure VII

4-Methoxy-o-phenylenediacetimide

4-Methoxy-o-phenylenediacetonitrile (135 gm., 0.725 m) was dissolved in acetic acid (180 ml.) and added dropwise during 30 minutes to a solution of hydrobromic acid in acetic acid (32%, 500 gm.) at 15—20°C. The reaction was stirred at room temperature for 4 hours. The precipitated solid was filtered and washed with acetic acid until the solid was colorless. The solid, a compound of Formula IX was washed with acetone and air dried. wt.=196 gm.

The above solid was added to water (3.5 *l.*) which had been preheated to 85°. When the solid had been dissolved anhydrous sodium acetate (48 gm., 0.59 m) was added during five minutes. The temperature rose to 93° and it was maintained at 92—93° for 1 hour. The heat source was removed and the reaction mixture was stirred for 45 minutes while the temperature dropped to 70°. The warm reaction was filtered to give the required imide. m.p. 180—183°, wt.=105 gm. The imide was recrystallized from absolute methanol m.p.=181—183°.

Anal. Calc. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83.
Found: C, 64.57; H, 5.59; N, 6.62.

The following examples of specific compounds and their preparation are given to illustrate the invention, it being understood that other compounds of the general formula may be made by routine modifications within the skill of the art.

EXAMPLE 1A

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine

Method I

4-Methoxy-o-phenylenediacetimide (50 gm., 0.245 m) was added portionwise during 20 minutes to a solution of borane in tetrahydrofuran (1 *l.*, 1 m in BH_3) which was being stirred at 10°C in an atmosphere of nitrogen. The solution was stirred at room temperature for 5 hours. Hydrochloric acid (6N, 20 ml.) was added to the stirred, ice-cooled reaction mixture during 45 minutes. The initial foaming subsided and a further 230 ml. of hydrochloric acid (6N) were added during 30 minutes. The suspension was stirred at room temperature for 16 hours and then the insolubles were filtered. The filtrate was evaporated to dryness at 15 mm. and the residual solid was treated with water (500 ml.). The aqueous mixture was filtered and the filtrate was basified with 10% sodium hydroxide solution. The precipitated oil was extracted into benzene (1 *l.*) and the benzene extract was dried over magnesium sulfate. Evaporation of the benzene afforded an oil (32 gm.) which was distilled at 0.05 mm. The fraction with the boiling range 90—93° was collected. wt.=28.0 gm.

The amine was analyzed as the maleate salt which was recrystallized from methyl ethyl ketone. m.p. 140—141°.

Anal. Calc. for $C_{11}H_{15}NO \cdot C_4H_4O_4$: C, 61.42; H, 6.53; N, 4.78.
Found: C, 61.52; H, 6.74; N, 4.93.

EXAMPLE 1B

Method II

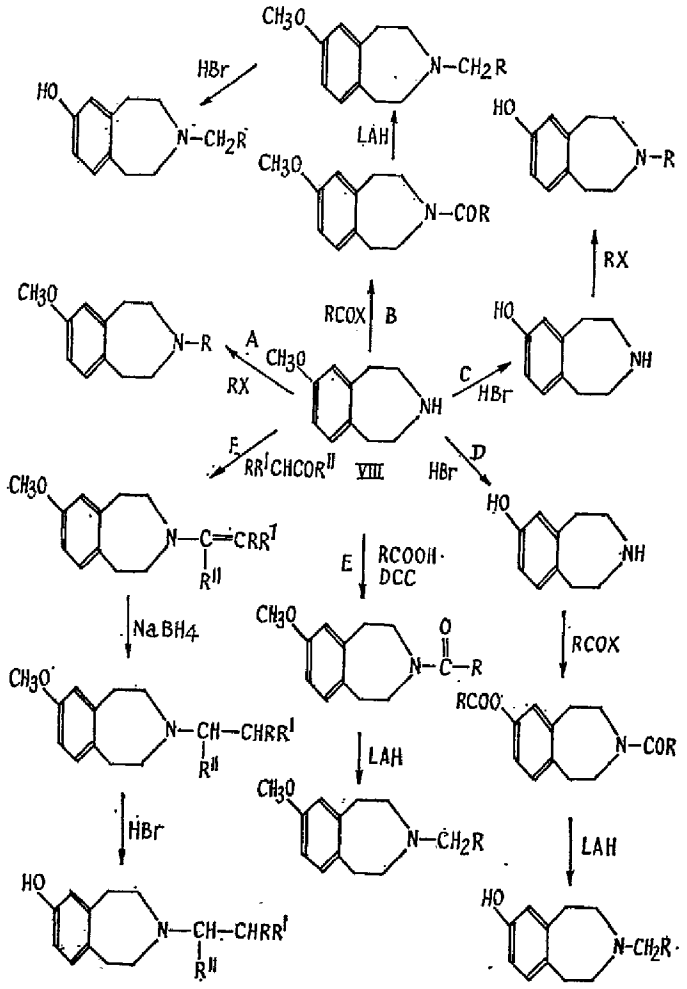
A Parr hydrogenation bomb (1 *l.*) was charged with 4-methoxy-o-phenylenediacetonitrile (75 gm., 0.403 m), absolute ethanol (500 ml.) and Raney-Nickel catalyst (Raney #28 in water, 50 gm. of wet catalyst). The catalyst was washed several times with absolute ethanol before it was added. The bomb was heated until the solution temperature was 90°C. and the hydrogen pressure was 1000 psi. Stirring was begun and heating was stopped. The reduction was carried out at 1000—700 psi and the stirring was continued until the temperature had dropped to 30°C. The

REACTION SCHEME B

Routes to 3-Substituted Benzazepines

hydrogen pressure reduction was 1760 psi. The catalyst was removed by filtration and the solvent was evaporated. The residual oil was distilled and the fraction with the boiling range 82—86° (0.01 mm) was collected. wt.=24 gm.

The following Reaction Scheme B illustrates graphically the techniques used to substituted various groups for a hydrogen atom in the 3- position in a benzazepine. In this scheme the groups R (which should not be confused with R used in formula I herein), R′ and R″ are intended either singly or in combination to designate the substituents appearing at position 3 in the numerous compounds according to the invention.



EXAMPLE 2

7-Hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine

(Demethylation)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (15 gm., 0.085 m) was refluxed with 48% aqueous hydrobromic acid (120 ml.) for 3 hours. The excess acid was evaporated in vacuo and the residual solid was washed with acetone and filtered to give the salt of the title compound. wt.=19.5 gm. The salt was recrystallized from absolute ethanol, m.p. 248—249°.

Anal. Calc. for $C_{10}H_{13}NO$. HBr: C, 49.19; H, 5.78; Br, 32.73; N, 5.74.

Found: C, 49.15; H, 6.00; Br, 32.44; N, 5.61.

The free amine was obtained by treating the above salt in aqueous solution with an equivalent amount of sodium hydroxide. The solid precipitate was filtered and recrystallized from isopropanol. m.p. 191—193°.

Anal. Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58.

Found: C, 73.34; H, 8.03; N, 8.71.

EXAMPLE 3

3-(3,3-Dimethylallyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method A)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (17.7 gm., 0.1 m), triethylamine (10.1 gm., 0.1 m) benzene (200 ml.) and dimethylformamide (40 ml.) were mixed and stirred at room temperature. 1-Chloro-3-methyl-2-butene (10.7 gm., 0.107 m) was added dropwise during 15 minutes. The reaction mixture was stirred for 4 hours and then water (200 ml.) was added. The benzene layer was separated and washed with water. After drying over magnesium sulfate the benzene was evaporated in vacuo to give an oil. wt.=20.5 gm. The oil was purified by chromatography on silica gel and elution with benzene:methanol (9:1). The pure amine (15.7 gm.) was converted to the hydrochloride salt and recrystallized from isopropanol. m.p. 204—206.5°.

Anal. Calc. for $C_{16}H_{23}NO$. HCl: C, 68.21; H, 8.58; N, 4.97; Cl, 12.58.

Found: C, 68.14; H, 8.69; N, 5.00; Cl, 12.71.

EXAMPLE 4

3-(3,3-Dimethylallyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method C)

Triethylamine (23.2 gm., 0.23 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (28 gm., 0.115 m) in dimethylformamide (120 ml.) which was being stirred at room temperature. After 5 minutes 1-chloro-3-methyl-2-butene (13.2 gm., 0.127 m) was added dropwise during 15 minutes. The reaction mixture was warmed to 50°C. for 2 hours. Water (200 ml.) was added and the product was isolated by extraction into diethyl ether. The ether extract was dried over magnesium sulfate and then the ether was evaporated to give a solid. The solid was triturated with cyclohexane and filtered to give the title compound. wt.=20 gm. The amine was converted to the hydrochloride salt and recrystallized from absolute methanol, m.p. 254.5—256°C.

Anal. Calc. for $C_{15}H_{21}NO$. HCl: 67.30; H, 8.28; N, 5.23; Cl, 13.24.

Found: C, 67.48; H, 8.34; N, 5.32; Cl, 13.39.

EXAMPLE 5

3-Cyclopropylmethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of cyclopropanecarboxylic acid chloride (10 gm., 0.0955 m) in tetrahydrofuran (50 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (13 gm., 0.0735 m) and pyridine (6.9 gm., 0.087 m) in tetrahydrofuran (100 ml.) at 0° during 30 minutes. The reaction mixture was stirred at room temperature for a further 2 hours. Water (200 ml.) was added and the tetrahydrofuran was evaporated in vacuo. The amide was extracted into diethyl ether and the ether layer was washed with 5% sodium hydroxide solution and hydrochloric acid (3N). After drying the ether extract over magnesium sulfate the solvent was evaporated in vacuo to give the amide.

The amide can be recrystallized from cyclohexane to give pure 3-cyclopropylcarbonyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine. m.p. 58—60°.

Anal. Calc. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71.

Found: C, 73.69; H, 7.79; N, 5.99.

The crude amide was dissolved in tetrahydrofuran (100 ml.) and added dropwise to a suspension of lithium aluminum hydride (2.5 gm., 0.066 m) in refluxing tetrahydrofuran (250 ml.) during 30 minutes. The reaction mixture was refluxed for a further 2 hours. The cooled reaction mixture was decomposed by the successive addition of water (2.5 ml.), 15% sodium hydroxide solution (2.5 ml.) and water (7.5 ml.). The tetrahydrofuran solution was filtered and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded the amine as an oil. wt.=13 gm. The amine was converted to the hydrochloride salt which was recrystallized from isopropanol. m.p. 222—223°.

Anal. Calc. for $C_{15}H_{21}NO$. HCl: C, 67.28; H, 8.28; N, 5.23; Cl, 13.24.

Found: C, 66.98; H, 8.16; N, 5.08; Cl, 13.00.

EXAMPLE 6

3-Cyclopropylmethyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method D)

Triethylamine (17.7 gm., 0.175 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (13 gm., 0.053 m) in dimethylformamide (50 ml.) which was being stirred at room temperature. After 5 minutes, the reaction mixture was cooled to 0°C. and cyclopropanecarboxylic acid chloride (13 gm., 0.124 m) was added dropwise during 10 minutes. The reaction mixture was

stirred as room temperature for 1 hour. Water (100 ml.) was added to the reaction and the precipitate was extracted into ethyl acetate (300 ml.). The ethyl acetate extract was washed with 10% sodium hydroxide solution and hydrochloric acid (3N). The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the crude product. wt.=14 gm. The product, 3-cyclopropylcarbonyl-7-cyclopropylcarbonyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine, was recrystallized from diisopropyl ether. m.p. 87—89°.

Anal. Calc. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68.
Found: C, 72.48; H, 6.99; N, 4.62.

A solution of 3-cyclopropylcarbonyl-7-cyclopropylcarbonyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine (18 gm., 0.06 m) in tetrahydrofuran (200 ml.) was added dropwise to a suspension of lithium aluminum hydride (5 gm., 0.132 m) in tetrahydrofuran (500 ml.) at room temperature during 30 minutes. The reaction mixture was stirred at room temperature for 18 hours. Ethyl acetate (50 ml.) was added cautiously, followed by a saturated aqueous solution (750 ml.) of ammonium tartrate. The reaction mixture was stirred for a further 1 hour. Two layers formed and the tetrahydrofuran layer was separated. The solvent was evaporated in vacuo and the residue was dissolved in chloroform. The chloroform solution was washed with water and dried over magnesium sulfate. Evaporation of the chloroform in vacuo afforded the title compound as a solid. wt.=12 gm. The amine was converted to the hydrochloride salt which was recrystallized from isopropanol m.p. 220—222°.

Anal. Calc. for $C_{14}H_{19}NO$. HCl: C, 66.24; H, 7.94; N, 5.52; Cl, 13.97.
Found: C, 66.13; H, 7.74; N, 5.30; Cl. 13.89.

Example 7

3-Cyclobutylmethyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method D)

Triethylamine (27.8 gm., 0.275 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (19.5 gm., 0.08 m) in dimethylformamide (90 ml.) which was being stirred at room temperature. After 5 minutes the reaction mixture was cooled to 0°C. and cyclobutanecarboxylic acid chloride (22 gm., 0.186 m) was added dropwise during 15 minutes. The reaction was stirred at room temperature for 3 hours. Water (200 ml.) was added to the reaction mixture and the precipitate was extracted into ethyl acetate (400 ml.). The ethyl acetate extract was washed with hydrochloric acid (3N) and sodium bicarbonate solution. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the crude product. wt.=26 gm. The product, 3-cyclobutylcarbonyl-7-cyclobutylcarbonyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine was recrystallized from diisopropyl ether. m.p. 96—98°.

Anal. Calc. for $C_{25}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28.
Found: C, 73.60; H, 7.64; N, 4.50.

A solution of 3-cyclobutylcarbonyl-7-cyclobutylcarbonyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine (18 gm., 0.055 m) in tetrahydrofuran (200 m.) was added dropwise to a suspension of lithium aluminum hydride (5 gm., 0.132 m) in tetrahydrofuran (500 ml.) at room temperature during 30 minutes. The reaction mixture was stirred at room temperature for 20 hours. Ethyl acetate (50 ml.) was added cautiously followed by a saturated aqueous solution (500 ml.) of ammonium tartrate. The reaction mixture was stirred for a further 1 hour. Two layers formed and the tetrahydrofuran layer was separated. The solvent was evaporated in vacuo and the residue was dissolved in chloroform. The chloroform solution was washed with water and dried over magnesium sulfate. Evaporation of the chloroform in vacuo afforded a semi-solid which was triturated with diethyl ether and filtered to give the title compound. wt.=9.3 gms.

The amine was converted to the hydrochloride salt which was recrystallized from methanol: diethyl ether. m.p. 252—254°.

Anal. Calc. for $C_{15}H_{21}NO$. HCl: C, 67.30; H, 8.28; N, 5.23; Cl, 13.24.
Found: C, 67.03; H, 8.06; N, 5.49; Cl, 13.00.

Example 8

3-Cyclopentylmethyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method D)

Triethylamine (19.4 gm., 0.191 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (12 gm., 0.049 m) in dimethylformamide (60 ml.) which was being stirred at room temperature. After 5 minutes, the reaction mixture was cooled to 0°C. and cyclopentanecarboxylic acid chloride (15.6 gm., 0.117 m) was added dropwise during 5 minutes. The reaction mixture was stirred at

room temperature for 3 hours. Water (200 ml.) was added and the precipitate was extracted into ethyl acetate (300 ml.). The ethyl acetate extract was washed with hydrochloric acid (3N) and sodium carbonate solution. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the crude amide-ester as an oil. wt.=17.5 gm.

The above oil (17.5 gm., 0.049 m) was dissolved in tetrahydrofuran (150 ml.) and the solution was added dropwise to a suspension of lithium aluminum hydride (3 gm., 0.079 m) in tetrahydrofuran (400 ml.) at room temperature during 30 minutes. The reaction mixture was stirred at room temperature for 17 hours. The complex was decomposed by the successive addition of water (3 ml.), 15% sodium hydroxide solution (3 ml.) and water (9 ml.). The resultant emulsion was treated with carbon dioxide until pH=8.5 had been attained. The tetrahydrofuran solution was filtered from the salts, dried over magnesium sulfate and evaporated in vacuo. The resultant oil was dissolved in refluxing diisopropyl ether (100 ml.) and on cooling the title compound precipitated as a crystalline solid. wt.=8 gm. The amine was converted to the hydrochloride salt which was recrystallized from absolute ethanol. m.p. 263—265°.

Anal. Calc. for: $C_{16}H_{23}NO$. HCl: C, 68.21; H, 8.58; N, 4.97; Cl, 12.58.
Found: C, 68.02; H, 8.49; N, 4.92; Cl, 12.58.

Example 9

3-Allyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method C)

Triethylamine (8.25 gm., 0.082 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (10 gm., 0.041 m) in dimethylformamide (35 ml.) which was being stirred at room temperature. After 5 minutes, allyl bromide (4.96 gm., 0.041 m) was added dropwise during 15 minutes. The reaction mixture was stirred at room temperature for 3 hours. Water (100 ml.) was added and the product was isolated by extraction into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound as a solid. wt.=6.4 gm. The amine was converted to the hydrochloride salt which was recrystallized from isopropanol. m.p. 176—178°.

Anal. Calc. for $C_{13}H_{17}NO$. HCl: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79.
Found: C, 64.82; H, 7.37; N, 5.59; Cl, 14.71.

Example 10

3-Cyclopentylmethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of cyclopentanecarboxylic acid chloride (9 gm., 0.068 m) in benzene (20 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (10 gm., 0.056 m) and triethylamine (5.65 gm., 0.056 m) in benzene (100 ml.) at 0° during 10 minutes. The reaction mixture was stirred at room temperature for 2 hours. Water (50 ml.) was added and the benzene extract was separated. The benzene extract was washed with hydrochloric acid (3N) and sodium carbonate solution and then it was dried over magnesium sulfate. Evaporation of the benzene in vacuo afforded 3-cyclopentylcarbonyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine as an oil. wt.=15 gm.

The crude amide was dissolved in tetrahydrofuran (60 ml.) and added dropwise to a suspension of lithium aluminum hydride (2.12 gm., 0.056 m) in tetrahydrofuran (90 ml.) during 30 minutes at room temperature. The reaction mixture was stirred at room temperature for 2.5 hours. The complex was decomposed by the successive addition of water (2.1 ml.), 15% sodium hydroxide solution (2.1 ml.) and water (6.3 ml.). The tetrahydrofuran solution was filtered and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded the amine as an oil which was converted to the hydrochloride salt, wt.=14.4 gm. The salt was recrystallized from isopropanol. m.p. 250—252°.

Anal. Calc. for $C_{17}H_{25}NO$. HCl: C, 69.03; H, 8.86; N, 4.74; Cl, 11.99.
Found: C, 68.87; H, 8.71; N, 4.98; Cl, 11.90.

Example 11

3-Cyclobutylmethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of cyclobutanecarboxylic acid chloride (8.05 gm., 0.068 m) in benzene (20 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-

benzazepine (10 gm., 0.056 m) and triethylamine (5.65 gm., 0.056 m) in benzene (100 ml.) at 0° during 10 minutes. The reaction mixture was stirred at room temperature for 2 hours. Water (50 ml.) was added and the benzene extract was separated. The benzene extract was washed with hydrochloric acid (3N) and sodium carbonate solution and then it was dried over magnesium sulfate. Evaporation of the benzene in vacuo afforded 3-cyclobutylcarbonyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine as an oil.

The crude amide was dissolved in tetrahydrofuran (60 ml.) and added dropwise to a suspension of lithium aluminum hydride (2.12 gm., 0.056 m) in tetrahydrofuran (90 ml.) during 30 minutes at room temperature. The reaction mixture was stirred at room temperature for 2.5 hours. The complex was decomposed by the successive addition of water (2.1 ml.), 15% sodium hydroxide solution (2.1 ml.) and water (6.3 ml.). The tetrahydrofuran solution was filtered and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded the amine as an oil which was converted to the hydrochloride salt. wt.=14.2 gm. The salt was recrystallized from isopropanol: methanol (10: 1). m.p. 235—236°.

Anal. Calc. for $C_{16}H_{23}NO$. HCl: C, 68.21; H, 8.58; N, 4.97; Cl, 12.58.
Found: C, 67.95; H, 8.64; N, 5.09; Cl, 12.64.

EXAMPLE 12

3-Allyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method A)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (5 gm., 0.0282 m), triethylamine (2.85 gm., 0.0282 m), benzene (30 ml.) and dimethylformamide were mixed and stirred at room temperature. A solution of 3-bromopropene (3.42 gm., 0.0282 m) in benzene (20 ml.) was added dropwise during 10 minutes. The reaction mixture was stirred at room temperature for 3 hours and then water (60 ml.) was added. The benzene layer was separated and washed with water. After drying over magnesium sulfate the benzene was evaporated in vacuo to give the title compound as an oil. The amine was converted to the hydrochloride salt. wt.=6.2 gm. The salt was recrystallized from methylethylketone: methanol (10: 1). m.p. 196—199°.

Anal. Calc. for $C_{14}H_{19}NO$. HCl: C, 66.24; H, 7.94; N, 5.52; Cl, 13.97.
Found: C, 66.49; H, 8.11; N, 5.67; Cl, 14.15.

EXAMPLE 13

7-Hydroxy-3-(2-methylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (Method C)

Triethylamine (8.25 gm., 0.082 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (10 gm., 0.041 m) in dimethylformamide (50 ml.) which was being stirred at room temperature. After 5 minutes methallyl chloride (3.72 gm., 0.041 m) was added dropwise during 15 minutes. The reaction mixture was warmed to 50° and stirred for 3 hours. Water (100 ml.) was added and the product was isolated by extraction into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound as a solid which was converted to the hydrochloride salt. wt.=8.5 gm. The salt was recrystallized from isopropanol: methanol (4: 1). m.p. 219—221°.

Anal. Calc. for $C_{14}H_{19}NO$. HCl: C, 66.24; H, 7.94; N, 5.52; Cl, 13.97.
Found: C, 66.01; H, 7.72; N, 5.49; Cl, 13.82.

EXAMPLE 14

7-Methoxy-3-propargyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method A)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (5 gm., 0.0282 m), triethylamine (2.85 gm., 0.0282 m), dimethylformamide (10 ml.) and benzene (40 ml.) were mixed and stirred at room temperature. A solution of 3-bromopropyne (3.45 gm., 0.029 m) in benzene (20 ml.) was added dropwise during 5 minutes. The reaction mixture was stirred at room temperature for 3 hours and then water (60 ml.) was added. The benzene layer was separated and washed with water. After drying over magnesium sulfate the benzene was evaporated in vacuo to give the title compound as an oil. The amine was converted to the hydrochloride salt. wt.=6.3 gm. The salt was recrystallized from methylethylketone: methanol (10: 1). m.p. 194—195°.

Anal. Calc. for $C_{14}H_{17}NO$. HCl: C, 66.77; H, 7.20; N, 5.56; Cl, 14.08.
Found: C, 66.68; H, 7.29; N, 5.43; Cl, 14.09.

EXAMPLE 15

7-Hydroxy-3-propargyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method C)

Triethylamine (8.7 gm., 0.0864 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (10.54 gm. 0.0432 m) in dimethylformamide (50 ml.) which was being stirred at room temperature. After 5 minutes, 3-bromopropyne (5.16 gm., 0.0432 m) was added dropwise during 5 minutes. The reaction mixture was stirred at room temperature for 4 hours. Water (100 ml.) was added and the product was isolated by extraction into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound as a solid which was converted to the hydrochloride salt. wt.=11.3 gm. The salt was recrystallized from isopropanol: methanol (1 : 1), m.p. 201—202°.

Anal. Calc. for $C_{13}H_{15}NO$. HCl: C, 65.69; H, 6.79; N, 5.89; Cl, 14.92.
Found: C, 65.89; H, 6.98; N, 6.01; Cl, 15.16.

EXAMPLE 16

7-Methoxy-3-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (10 gm., 0.0565 m) was dissolved in a solution of formalin 24 ml.) and formic acid (28 ml.) and refluxed for 6 hours. After standing at room temperature for 16 hours, the solvents were evaporated in vacuo and the residue was shaken with 10% sodium hydroxide solution and diethyl ether. The ether extract was washed with water and dried over magnesium sulfate. Evaporation of the ether in vacuo afforded the title compound as an oil which was converted to the hydrochloride salt. wt.=10.0 gm. The salt was recrystallized from methylethylketone: methanol. m.p. 188—190°.

Anal. Calc. for $C_{12}H_{17}NO$. HCl: C, 63.29; H, 7.97; N, 6.15; Cl, 15.57.
Found: C, 63.16; H, 7.74; N, 6.08; Cl, 15.80.

EXAMPLE 17

7-Hydroxy-3-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

7-Methoxy-3-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine (16 gm., 0.0837 m) was dissolved in 48% aqueous hydrobromic acid (120 ml.) and refluxed for 3 hours. The excess acid and water were evaporated in vacuo. The solid residue was dissolved in water and basified with saturated sodium carbonate solution. The precipitated product was extracted into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound as a solid which was recrystallized from diisopropyl ether: methanol. m.p. 142—146°, wt.=11 gm. The amine was converted to the hydrochloride salt. wt.=10.8 gm. The salt was recrystallized from methanol. m.p. 244—248°.

Anal. Calc. for $C_{11}H_{15}NO$. HCl: C, 61.81; H, 7.55; N, 6.56; Cl, 16.59.
Found: C, 61.81; H, 7.62; N, 6.47; Cl, 16.72.

EXAMPLE 18

3-Ethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of acetyl chloride (13.4 gm., 0.170 m) in benzene (50 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (23.8 gm., 0.134 m) and pyridine (13.7 gm., 0.174 m) in benzene (200 ml.) at room temperature during 15 minutes. The reaction mixture was stirred at room temperature for 2 hours. Water (100 ml.) was added and the benzene extract was separated and dried over magnesium sulfate. Evaporation of the benzene in vacuo afforded 3-acetyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine which crystallized from diisopropyl ether (150 ml.) m.p. 90—91°. wt.=26 gm.

Anal. Calc. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.
Found: C, 71.25; H, 7.87; N, 6.26.

A solution of 3-acetyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (16.0 gm., 0.073 m) in tetrahydrofuran (50 ml.) was added dropwise to a suspension of lithium aluminum hydride (3.0 gm., 0.079 m) in tetrahydrofuran (200 ml.) during 30 minutes at room temperature. The reaction mixture was then refluxed for 2 hours. The complex was decomposed by the successive addition of water (3 ml.), 15% sodium hydroxide solution (3 ml.) and water (9 ml.). The tetrahydrofuran solution was filtered and dried over magnesium sulfate. Evaporation of the solvent in vacuo

afforded the amine as an oil which was converted to the hydrochloride salt and recrystallized from methanol-diethyl ether (1:1). m.p. 219—221°. wt.=12.5 gm.

Anal. Calc. for $C_{13}H_{19}NO$. HCl: C, 64.58; H, 8.34; N, 5.79; Cl, 14.66.
Found: C, 64.55; H, 8.52; N, 5.91; Cl, 14.63.

EXAMPLE 19

3-Ethyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

3-Ethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (15 gm., 0.073 m) was dissolved in 48% aqueous hydrobromic acid (250 ml.) and refluxed for 3 hours. The excess acid and water were evaporated in vacuo. The solid residue was dissolved in water and basified with saturated sodium carbonate solution. The precipitated product was extracted into chloroform. The chloroform layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound as a solid which was recrystallized from 50% aqueous ethanol. m.p. 168—171°. wt.=11.3 gm. The amine was converted to the hydrochloride salt and recrystallized from methanol: diethyl ether (1:1), m.p. 247—250°, wt.=11.2 gm.

Anal. Calc. for $C_{12}H_{17}NO$. HCl: C, 63.29; H, 7.97; N, 6.15; Cl, 15.57.
Found: C, 63.51; H, 7.87; N, 6.01; Cl, 15.80.

EXAMPLE 20

7-Methoxy-3-n-propyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of propionyl chloride (6.5 gm., 0.07 m) in tetrahydrofuran (20 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (12 gm., 0.0676 m) and triethylamine (7.04 gm., 0.07 m) in tetrahydrofuran (100 ml.) at 0° during 15 minutes. The reaction mixture was stirred at room temperature for 4 hours. Water (100 ml.). was added and the tetrahydrofuran was evaporated in vacuo. The aqueous residue was extracted with ethyl acetate. The ethyl acetate extract was washed with hydrochloric acid (3N) and 10% sodium hydroxide solution. After drying the ethyl acetate layer over magnesium sulfate the solvent was evaporated in vacuo to give the amide 7-methoxy-3-propionyl-1,2,4,5-tetrahydro-3H,3-benzazepine as an oil.

The crude amide was dissolved in tetrahydrofuran (50 ml.) and added dropwise to a suspension of lithium aluminum hydride (2.56 gm., 0.0676 m) in tetrahydrofuran at room temperature during 30 minutes. The reaction mixture was stirred at room temperature for 3 hours. The complex was decomposed by the successive addition of water (2.56 ml.), 15% sodium hydroxide solution (2.56 ml.) and water (7.68 ml.). The tetrahydrofuran solution was filtered and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded the title compound as an oil. wt.=14 gm. The amine was converted to the hydrochloride salt and recrystallized from methylethylketone, m.p. 208—210°.

Anal. Calc. for $C_{14}H_{21}NO$. HCl: C, 65.73; H, 8.67; N, 5.48; Cl, 13.86.
Found: C, 65.69; H, 8.67; N, 5.54; Cl, 13.92.

EXAMPLE 21

7-Hydroxy-3-n-propyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

7-Methoxy-3-n-propyl-1,2,4,5-tetrahydro-3H,3-benzazepine (13 gm., 0.059 m) was dissolved in 48% aqueous hydrobromic acid (100 ml.) and refluxed for 3 hours. The excess acid and water were evaporated in vacuo. The solid residue was dissolved in water and basified with saturated sodium carbonate solution. The precipitated product was extracted into ethyl acetate. The ethyl acetate extract was dried over magnesium sulfate and evaporated in vacuo to give a solid which was triturated with diisopropyl ether and filtered. m.p. 146—148°. wt.=9 gm. The amine was converted to the hydrochloride salt and recrystallized from isopropanol. m.p. 208—212°.

Anal. Calc. for $C_{13}H_{19}NO$. HCl: C, 64.58; H, 8.34; N, 5.79; Cl, 14.66.
Found: C, 64.68; H, 8.38; N, 5.53; Cl, 14.60.

EXAMPLE 22

7-Methoxy-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

A solution of phenylacetyl chloride (15.5 gm., 0.10 m) chloroform (25 ml.) was added dropwise to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (14.6 gm., 0.08 m) and pyridine (9.25 gm., 0.12 m) in chloroform (100 ml.) at 0°C.

during 45 minutes. The reaction mixture was stirred at room temperature for 5 hours. Water (300 ml.) was added and the chloroform extract was separated and dried over magnesium sulfate. Evaporation of the chloroform in vacuo afforded a solid which was triturated with isoproponal and filtered to give the crude amide 7-methoxy-3-phenylacetyl-1,2,4,5-tetrahydro-3H,3-benzazepine. m.p. 85.5—86.5°. wt.=11.4 gm. The amide was recrystallized from isopropanol: diisopropyl ether (3:1). m.p. 86.5—87.5°.

Anal. Calc. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74.
Found: C, 77,25; H, 6.93; N, 4.90.

A solution of 7-methoxy-3-phenylacetyl-1,2,4,5-tetrahydro-3H,3-benzazepine (10.25 gm., 0.034 m) in tetrahydrofuran (45 ml.) was added dropwise to a suspension of lithium aluminum hydride (3.0 km., 0.079 m) in diethyl ether (75 ml.) during 1 hour at room temperature. The reaction mixture was refluxed for 2 hours. The complex was decomposed by the successive addition of water (3 ml.), 15% sodium hydroxide solution (3 ml.) and water (9 ml.). The solution was filtered from the salts and dried over magnesium sulfate. Evaporation of the solvents in vacuo afforded the amine as an oil. wt.=9.8 gm. The amine was converted to the hydrochloride salt and recrystallized from isopropanol. m.p. 206.5—207.5°.

Anal. Calc. for $C_{19}H_{23}NO$. HCl: C, 71.76; H, 7.92; N, 4.59; Cl, 11.18.
Found: C, 71.80; H, 7.61; N, 4.41; Cl, 11.15.

EXAMPLE 23

7-Hydroxy-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine (Method B)

7-Methoxy-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine (9.8 gm., 0.034 m) was dissolved in 48% aqueous hydrobromic acid (100 ml.) and refluxed for 2 hours. The excess acid and water were evaporated in vacuo. The solid residue was dissolved in water and basified with saturated sodium carbonate solution. The precipitated solid was filtered and dried. wt.=9 gm. The amine was converted to the hydrochloride salt and recrystallized from water. m.p. 100—102°. wt.=7 gm.

Anal. Calc. for $C_{18}H_{21}NO$. HCl: C, 71.15; H, 7.30; N, 4.61; Cl, 11.67.
Found: C, 71.10; H, 7.23; N, 4.90; Cl, 11.58.

EXAMPLE 24

7-Methoxy-3-(1-methyl-2-phenylethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (Method F)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (13 gm., 0.0735 m), 1-phenyl-2-propanone (11 gm., 0.082 m) and p-toluenesulfonic acid (0.3 gm.) were dissolved in toluene (100 ml.) and refluxed for 64 hours. The toluene was condensed above a Soxhlet extractor, containing molecular sieves (type 4A), which was attached to a Dean and Stark apparatus. The toluene solution was diluted with absolute methanol (200 ml.) and cooled to 10°C. Sodium borohydride (10 gm., 0.26 m) was added portionwise to the stirred reaction mixture during 15 minutes. The reaction mixture was stirred at room temperature for 4 hours. Water (500 ml.) was added cautiously. The toluene layer was separated and the aqueous solution was further extracted with diethyl ether (300 ml.). The combined ether and toluene extracts were washed with water and then dried over magnesium sulfate. Evaporation of the solvents in vacuo afforded an oil. wt.=22 gm. The oil was purified by chromatography on silica gel. Elution of the column with methanol: benzene (1:9), afforded the title compound as an oil which was converted to the hydrochloride salt and crystallized from acetone: diethyl ether (1:1). m.p. 172—182°. wt.=12.5 gm. The salt was recrystallized from acetone. m.p. 179—182°. wt.=7 gm.

Anal. Calc. for $C_{20}H_{25}NO$. HCl: C, 72.38; H, 7.90; N, 4.22; Cl, 10.68.
Found: C, 72.61; H, 7.86; N, 4.30; Cl, 10.61.

EXAMPLE 25

7-Hydroxy-3-(1-methyl-2-phenylethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine

7 - Methoxy - 3 - (1 - methyl - 2 - phenylethyl) - 1,2,4,5 - tetrahydro - 3H,3 - benzazepine hydrochloride (13.0 gm., 0.039 m) was suspended in 48% aqueous hydrobromic acid (180 ml.) and refluxed with vigorous stirring for 7 hours. The cooled reaction mixture was filtered and the precipitate was washed with water and acetone. m.p. 240—250°. wt.=13.5 gm. The solid was dissolved in dimethylformamide: water (50 ml: 1 l.) and sodium hydroxide solution (50%, 3.12 gm.) was added. The precipitated gum was extracted into chloroform and the chloroform solution was dried

over magnesium sulfate. Evaporation of the chloroform in vacuo afforded the title compound as an oil. The amine was converted to the hydrochloride salt and recrystallized from methanol m.p. 273—283° (d). wt.=8 gm.

Anal. Calc. for $C_{19}H_{23}NO$. HCl: C, 71.80; H, 7.61; N, 4.41; Cl, 11.16.
Found: C, 72.09; H, 7.78; N, 4.71; Cl, 11.17.

EXAMPLE 26

3-(p-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method E)

A solution of p-nitrophenylacetic acid (11.7 gm., 0.064 m) in tetrahydrofuran (50 ml.) was added to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (10.3 gm., 0.058 m) in tetrahydrofuran (50 ml.) at room temperature. A solution of dicyclohexylcarbodiimide (14.5 gm., 0.0705 m) in tetrahydrofuran (50 ml.) was added immediately to the reaction mixture and stirring was continued for 4 hours. Acetic acid (10 ml.) was added to the reaction mixture and then the solids were removed by filtration. The solvent was evaporated in vacuo and the residue was treated with diethyl ether (150 ml.) and benzene (150 ml.). The insoluble solids were removed by filtration and washed with benzene (200 ml.). The solids were dissolved in tetrahydrofuran (250 ml.) and filtered from a small quantity of dicyclohexyl urea. The benzene:ether extract was washed with potassium carbonate solution, and hydrochloric acid (3N). The tetrahydrofuran extract was washed with potassium carbonate solution. The extracts were combined and evaporated in vacuo to give the crude amide 3-(*p*-nitrophenylacetyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine. wt.=25 gm. The crude amide was dissolved in methanol (200 ml.) and hydrogenated at 60 psi over platinum oxide (1 gm.). Hydrogen absorption ceased after 20 minutes with a drop in pressure of 17 psi. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in hydrochloric acid (0.3N, 1500 ml.) and filtered from some insolubles. The acid solution was washed with ether and then it was basified with sodium hydroxide solution. The precipitated product was extracted into chloroform. The chloroform extract was dried over magnesium sulfate and evaporated in vacuo to give the crude amino-amide 3-(p-aminophenylacetyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine. wt.=22.5 gm. The amino-amide was dissolved in tetrahydrofuran (150 ml.) and added dropwise to a suspension of lithium aluminum hydride (5 gm., 0.0132 m) in diethyl ether (175 ml.) at such a rate that gentle reflux was maintained. The reaction mixture was refluxed for 21 hours. The complex was decomposed by the successive addition of water (5 ml.), 15% sodium hydroxide solution (5 ml.) and water (15 ml.). The solvents were filtered and dried over magnesium sulfate. Evaporation of the solvents in vacuo afforded an oil which was converted to the dihydrochloride salt and recrystallized from methanol to give the dihydrochloride of the title compound. m.p. 264.5—265.5. wt.=11.1 gm.

Anal. Calc. for $C_{19}H_{24}N_2O$. 2HCl: C, 61.79; H, 7.10; N, 7.59; Cl, 19.20.
Found: C, 61.63; H, 6.86; N, 7.61; Cl, 19.45.

EXAMPLE 27

3-(p-Aminophenethyl)7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (Method E)

3-(p-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine dihydrochloride (11.3 gm., 0.0306 m) was suspended in 48% aqueous hydrobromic acid (175 ml.) and refluxed for 2 hours. The excess acid and water were removed in vacuo. The residual solid was dissolved in water (250 ml.) and basified with potassium carbonate solution. The precipitated solid was filtered and dried. The solid was converted to the hydrochloride salt and recrystallized from methanol:diethyl ether (1:2). m.p. 309.5—311.5°. wt.=8.7 gm.

Anal. Calc. for $C_{18}H_{22}N_2O$. 2HCl: C, 60.84; H, 6.81; N, 7.89; Cl, 19.95.
Found: C, 60.62; H, 7.03; N, 8.06; Cl, 19.85.

EXAMPLE 28

7-(Methoxy-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (Method A)

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (10 gm., 0.0564 m), triethylamine (5.65 gm., 0.0564 m), dimethylformamide (20 ml.) and benzene (80 ml.) were mixed and stirred at room temperature. A solution of 3-chloropropenylbenzene (8.6 gm., 0.0564 m) in benzene (30 ml.) was added dropwise during 5 minutes. The

reaction mixture was stirred for 4 hours and then water (200 ml.) was added. The benzene layer was separated and washed with water. After drying over magnesium sulfate the benzene was evaporated in vacuo to give an oil. The oil was purified by chromatography on silica gel and elution with benzene:methanol (4:1). The pure amine 10.1 gm.) was converted to the hydrochloride salt and recrystallized from methylethylketone:methanol (15:1). m.p. 198—200°. wt.=9.4 gm..

Anal. Calc. for $C_{20}H_{23}NO$. HCl: C, 72.81, H, 7.33; N, 4.25; Cl, 10.75.
Found: C, 72.79; H, 7.39; N, 4.20; Cl, 10.84.

EXAMPLE 29

7-Hydroxy-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (Method C)

Triethylamine (8.15 gm., 0.082 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (10 gm., 0.041 m) in dimethylformamide (35 ml.). After 5 minutes 3-chloropropenylbenzene (6.25 gm., 0.041 m) was added dropwise during 15 minutes. The reaction mixture was stirred at room temperature for 4 hours. Water was added and the product was isolated by extraction into ethyl acetate. The ethyl acetate extract was dried over magnesium sulfate and then the solvent was evaporated in vacuo to give the title compound as a solid which was recrystallized from diisopropyl ether:methanol (5:1), m.p. 158—159°, wt.=8.1 gm.

Anal. Calc. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01
Found: C, 81.63; H, 7.87; N, 5.28.

EXAMPLE 30

7-Hydroxy-3(trans-2-phenylcyclopropylmethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (Method D)

Triethylamine (15.5 gm., 0.154 m) was added to a solution of 7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide (12.5 gm., 0.0512 m) in dimethylformamide (100 ml.) which was being stirred at room temperature. After 5 minutes, trans-2-phenylcyclopropane carboxylic acid chloride (18.45 gm., 0.1024 m) was added dropwise during 20 minutes. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate (400 ml.) and water (200 ml.). The ethyl acetate extract was washed with hydrochloric acid (3N) and sodium bicarbonate solution. The ethyl acetate layer was dried over magnesium sulfate and evaporated in vacuo to give a gum. wt.=18 gm. This material was dissolved in tetrahydrofuran (100 ml.) and the solution was added dropwise to a suspension of lithium aluminum hydride (3.9 gm., 0.1024 m) in tetrahydrofuran (100 ml.) during 30 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours. Ethyl acetate (15 ml.) was added cautiously followed by a saturated aqueous solution of ammonium tartrate (200 ml.). The tetrahydrofuran layer was separated and evaporated in vacuo. The residue was dried by azeotroping with benzene (750 ml.) and then the solid was triturated with acetone and filtered to give the title compound. wt.=12.55 gm. The amine was recrystallized from methanol. m.p. 190—192°. wt.=10.4 gm.

Anal Calc. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77.
Found: C, 81.73; H, 7.90; N, 4.77.

EXAMPLE 31

3-(β-Actoxyethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (12 gm., 0.068 m) and ethylene oxide (4 gm., 0.091 m) were dissolved in methanol at −40°C. The solution was stirred as the temperature rose to room temperature during 6 hours. The excess ethylene oxide and solvent were evaporated in vacuo and an oil was obtained. The oil can be crystallized from diisopropyl ether to give 3-(β-hydroxyethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine. m.p. 79—80°.

Anal. Calc. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33.
Found: C, 70.34; H, 8.33; N, 6.56.

The crude alcohol was dissolved in pyridine (25 ml.) and the solution was cooled to 10°C. Acetic anhydride (9 ml.) was added and the reaction was allowed to stand at room temperature for 16 hours. Evaporation of the pyridine and acetic anhydride in vacuo afforded a gum which was dissolved in water. The solution was basified with sodium carbonate solution and the precipitated oil was extracted into diethyl ether.

Evaporation of the ether afforded an oil which was a mixture of the required ester and the alcohol. The oil was dissolved in benzene and acetyl chloride (1 ml.) was added. After 3 hours at room temperature the solvent was evaporated in vacuo and the residue was suspended in diethyl ether and treated with hydrogen chloride. The precipitated hydrochloride salt was filtered and recrystallized from methylethylketone. m.p. 155—157°. wt.=8 gm.

Anal. Calc. for $C_{15}H_{21}NO_3$. HCl: C, 60.07; H, 7.40; N, 4.67; Cl, 11.82.
Found: C, 59.96; H, 7.31; N, 4.87; Cl, 11.82.

EXAMPLE 32

3-(β-Acetoxyethyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine

7-Hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (13.98 gm., 0.0855 m) and triethylamine (17.9 gm., 0.18 m) were dissolved in dimethylformamide (60 ml.) and the solution was heated and stirred to 100°. 2-Chloroethylacetate (22 gm., 0.18 m) was added dropwise during 5 minutes. After 5 hours at 100° the reaction mixture was cooled and diluted with ethyl acetate (300 ml.). The ethyl acetate extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded an oil. The oil was extracted with hot diisopropyl ether and the resultant solution was cooled to −70°C. A gum precipitated and the supernatant solvent was decanted from it. The solution precipitated a small quantity (1.3 gm.) of the required ester. The solvent was evaporated in vacuo and the residue was combined with the gum from above and chromatogrammed on silica gel. Elution with benzene: methanol (9:1) afforded the required ester (4.7 gm.) as a gum. The combined products (1.3 gm. + 4.7 gm.) were converted to the oxalate salt which was recrystallized from methanol: ether (2:1). m.p. 161—163°.

Anal. Calc. for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N. 4.13.
Found: C, 56.76; H, 6.25; N, 4.38.

EXAMPLE 33

3-(β-Acetoxypropyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine

7-Hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine (13 gm., 0.08 m) was suspended in methanol (200 ml.) at reflux. 1,2-propylene oxide (5.55 gm., 0.096 m) was added dropwise during 10 minutes and the reaction mixture was stirred and refluxed for further 15 minutes. An additional portion of 1,2-propylene oxide (1.66 gm., 0.0286 m) was added and the reaction was continued for 1½ hours. The excess reagent and methanol were evaporated in vacuo and the residue was crystallized from a mixture of methanol (35 ml.) and ethyl acetate (100 ml.) m.p. 162—166°. The alcohol 7-hydroxy-3-(β-hydroxypropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine was recrystallized from ethyl acetate. m.p. 164—166°.

Anal. Calc. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33.
Found: C, 70.63; H, 8.63; N, 6.29.

Benzyl bromide (13.7 gm., 0.08 m) was added dropwise to a solution of 7-hydroxy-3-(β-hydroxypropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (14.7 gm., 0.0665 m) and potassium hydroxide (3.92 gm., 0.07 m) in absolute ethanol (80 ml.) at reflux, during 1.5 hours. The reaction mixture was refluxed a further 1.5 hours. The precipitated potassium bromide was filtered and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate and water. The ethyl acetate extract was separated and dried over magnesium sulfate. Evaporation of the ethyl acetate afforded an oil. wt.=20.4 gm. The oil was chromatogrammed on silica gel and elution of the column with methanol: benzene (1:9) afforded the pure compound 7-benzyloxy-3-(β-hydroxypropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine as an oil which solidified. m.p. 66—70°. wt.=14 gm. The product was recrystallized from petroleum ether (40—60°). m.p. 73—75°.

Anal. Calc. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50.
Found: C, 77.20; H, 7.95; N, 4.64.

7-Benzyloxy-3-(β-hydroxypropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine (14 gm., 0.045 m) and triethylamine (5.05 gm., 0.05 m) were dissolved in benzene (100 ml.) and the solution was cooled to 10°. Acetyl chloride (3.92 gm., 0.05 m) was added dropwise to the stirred reaction mixture during 15 minutes. After stirring the reaction mixture for 2 hours at room temperature the benzene solution was filtered from the triethylamine hydrochloride. The benzene solution was washed with water, and sodium carbonate solution and then it was dried over magnesium sulfate. Evaporation of the benzene in vacuo afforded the crude ester 7-benzyloxy-3-(β-acetoxypropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine. wt.=14 gm. The ester was hydrogenated in acetic acid

solution (200 ml.) over 5% palladium charcoal (2 gm.) at 50 psi and at room temperature. After 8 hours the absorption of hydrogen had ceased and the catalyst was removed by filtration. The acetic acid was evaporated in vacuo and the residue was dissolved in chloroform. The chloroform solution was washed with sodium carbonate solution and water. Evaporation of the chloroform in vacuo afforded the title compound as an oil. wt.=10.2 gm. The oil was converted to the oxalate salt and recrystallized from methanol. m.p. 195—197°. wt.=6.5 gm.

Anal. Calc. for $C_{17}H_{23}NO_7$: C, 57.78, H, 6.56; N, 3.96.
Found: C, 58.03; H, 6.51; N, 3.84.

EXAMPLE 34

3-(2-p-Aminophenyl-1-methylethyl)-7-methoxy,1,2,4,5-tetrahydro-3H,3-benzazepine

7-Methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (10 gm., 0.0565 m), 1-(*p*-nitrophenyl)-2-propanone (11 gm., 0.062 m) and *p*-toluenesulfonic acid (0.2 gm.) were dissolved in toluene (100 ml.) and refluxed for 20 hours. A Dean and Stark apparatus was attached and the eliminated water was collected. The toluene solution was diluted with methanol (200 ml.) and cooled to 10°. Sodium borohydride (8.5 gm., 0.226 m) was added portionwise to the stirred reaction during 20 minutes. The reaction mixture was stirred at room temperature for 4 hours. Water (100 ml.) and diethyl ether (100 ml.) were added cautiously. The oganic layer was separated and washed with dilute hydrochloric acid. A gummy precipitate formed which was separated and then basified with sodium hydroxide solution. The aqueous acid solution was also basified. The alkali insolubles were combined and extracted into diethyl ether. The ether solution was dried over magnesium sulfate. Evaporation of the solvent afforded a dark red oil. wt.=10.6 gm. The oil was purified by chromatography on silica gel. Elution of the column with benzene: diethyl ether (1:1) afforded 7-methoxy-3-[1-methyl-2-*p*-nitrophenylethyl]-1,2,4,5-tetrahydro-3H,3-benzazepine as an oil. The amine was converted to the hydrochloride salt and recrystallized from methanol. m.p.=223—230°. wt.=3.9 gm.

Anal. Calc. for $C_{20}H_{24}N_2O_3$. HCl: C, 63.74; H, 6.69; N, 7.43; Cl, 9.41.
Found: C, 63.77; H, 6.69; N, 7.48; Cl, 9.72.

The amine hydrochloride (2.4 gm., 0.0064 m) was dissolved on methanol (75 ml.) containing conc. hydrochloric acid (1 ml.) and the solution was charged with 5% palladium-charcoal catalyst. The nitro group was hydrogenated at 50 psi during 15 minutes. The solution was filtered from the catalyst and evaporated to give the crude title compound as the dihydrochloride salt. The salt was purified by crystallization from methanol: diethyl ether (2:1). m.p.=245—255°.

Anal. Calc. for $H_{20}H_{26}N_2O$. 2HCl: C, 62.65; H, 7.36; N, 7.31; Cl, 18.50.
Found: C, 62.47; H, 7.51; N, 7.33; Cl, 18.13.

EXAMPLE 35

3-(p-Acetamidophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine

Triethylamine (11.0 gm. 0.108 m) was added to a suspension of 3-(*p*-aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine dihydrochloride (13 gm., 0.035 m) in chloroform (200 ml.). The mixture was stirred and cooled with an ice-water bath. Acetyl chloride (3.3 gm., 0.042 m) was added dropwise during 5 minutes and the reaction mixture was stirred at room temperature for 1 hour. The insoluble material was filtered to give the title compound as the hydrochloride salt, m.p.=289—290°. wt.=8.0 gm.

Anal. Calc. for $C_{21}H_{26}N_2O_3$. HCl: C, 67.28; H, 7.26; N, 7.47; Cl, 9.46.
Found: C, 67.10; H, 7.56; N, 7.53; Cl, 9.34.

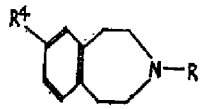
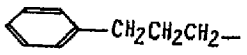
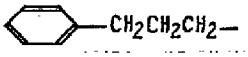
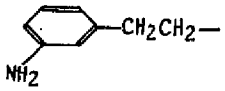
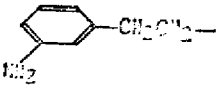
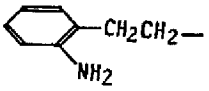
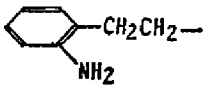
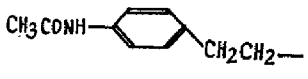
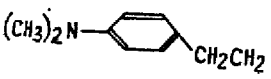
EXAMPLE 36

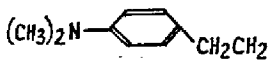
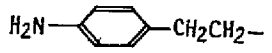
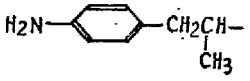
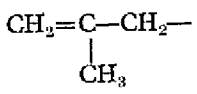
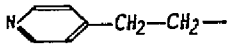
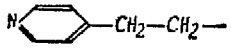
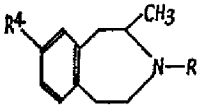
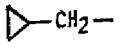
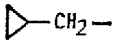
7-Methoxy-3[2-(4-phenyl-1-piperazinyl)-ethyl]-1,2,4,5-tetrahydro-3H,3-benzazepine

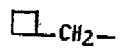
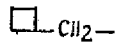
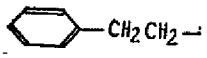
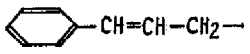
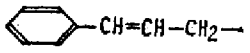
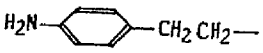
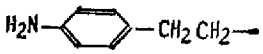
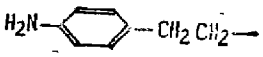
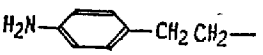
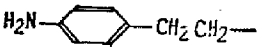
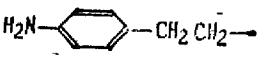
A solution of 2-(4-phenyl-1-piperazinyl) ethyl chloride (16.5 gm., 0.074 m) in benzene (50 ml.) was added dropwise during 30 minutes to a solution of 7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (11.9 gm., 0.067 m), triethylamine (7.5 gm., 0.074 m) and dimethylformamide (30 ml.) in benzene (90 ml.) at room temperature. The reaction mixture was stirred at room temperature for 6 hours and then at reflux for 24 hours. The cooled reaction mixture was diluted with water and the benzene layer was separated, dried over magnesium sulfate and evaporated in vacuo. The residual oil solidified and the solid was crystallized from isopropanol to give the title compound. m.p.=103—4°. wt.=9.2 gm.

The amine was converted to the dihydrochloride salt in methanol solution and was recrystallized from methanol. m.p. = 282—6° (d).

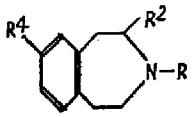
Anal. Calc. for $C_{23}H_{31}N_3O \cdot 2HCl$: C, 61.94; H, 7.65; N, 9.43; Cl, 15.91.
Found: C, 62.16; H, 7.88; N, 9.64; Cl, 15.92.

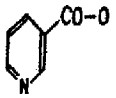
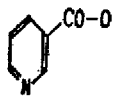
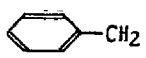
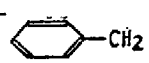
		Additional Examples
R^4	R	
CH_3O	$CH_3—CH=CH—CH_2—$	3-(3-Methylallyl)-7-methoxy-1,2,4,4-tetrahydro-3H,3-benzazepine
HO	$CH_3—CH=CH—CH_2—$	7-Hydroxy-3-(3-methylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		7-Methoxy-3-(3-phenylpropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		7-Hydroxy-3-(3-phenylpropyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-(*m*-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-(*m*-Aminophenethyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-(*o*-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-(*o*-Aminophenethyl)-7-hydroxy-1,2,4,5,-tetrahydro-3H,3-benzazepine
HO		3-(*p*-Acetamidophenethyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		7-Methoxy-3-(*p*-methylaminophenethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		7-Hydroxy-3-(*p*-methylaminophenethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-(*p*-Dimethylaminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine

R^4	R	Additional Examples
HO		3-(*p*-Dimethylaminophenethyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
H		3-(*p*-Aminophenethyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-(2-*p*-Aminophenyl-1-methyl-ethyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		7-Methoxy-3-(2-methylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		7-Methoxy-3-[2-(4-pyridyl)-ethyl]-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		7-Hydroxy-3-[2-(4-pyridyl) ethyl]-1,2,4,5-tetrahydro-3H,3-benzazepine
		
CH_3O	$(CH_3)_2C=CH-CH_2-$	3-(3,3-Dimethylallyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)_2C=CH-CH_2-$	(+)-3-(3,3-Dimethylallyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)_2C=CH-CH_2-$	(−)-3-(3,3-Dimethylallyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	3-(3,3-Dimethylallyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	(+)-3-(3,3-Dimethylallyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	(−)-3-(3,3-Dimethylallyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-Cyclopropylmethyl-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-Cyclopropylmethyl-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

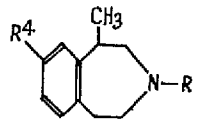
R^4	R	Additional Examples
CH_3O		3-Cyclobutylmethyl-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-Cyclobutylmethyl-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$CH_2=CH-CH_2-$	3-Allyl-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$CH_2=CH-CH_2-$	3-Allyl-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$CH_2=C(CH_3)-CH_2-$	8-Methoxy-2-methyl-3-(2-methylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$CH_2=C(CH_3)-CH_2-$	8-hydroxy-2-methyl-3-(2-methylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		8-Methoxy-2-methyl-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		8-hydroxy-2-methyl-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		8-Methoxy-2-methyl-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		8-Hydroxy-2-methyl-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-(*p*-Aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		(+)-3-(*p*-Aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		(−)-3-(*p*-Aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-(*p*-Aminophenethyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		(+)-3-(*p*-Aminophenethyl-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		(−)-3-(*p*-Aminophenethyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

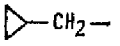
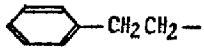
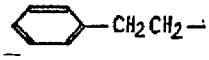
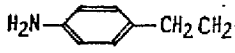
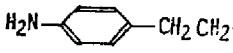
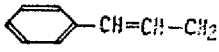
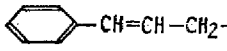
R^4	R	Additional Examples
CH_3O	H	8-Methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	H	8-Hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
H	H	2-Methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

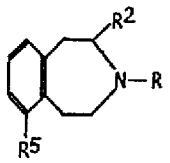


R^4	R	R^2	Additional Examples
CH_3OCH_2O	$(CH_3)_2C=CH-CH_2$	H—	O-Methoxymethyl-3-(3,3-dimethylallyl)-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3OCH_2O	$(CH_3)_2C=CH-CH_2$	CH_3—	O-Methoxymethyl-3-(3,3-dimethylallyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
	$(CH_3)_2C=CH-CH_2$	H—	3-(3,3-Dimethylallyl)-7-nicotinoyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine
	$(CH_3)_2C=CH-CH_2-$	CH_3	3-(3,3-Dimethylallyl)-2-methyl-8-nicotinoyloxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)C=CH-CH_2-$		3-(3,3-Dimethylallyl)-8-methoxy-2-phenyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$		3-(3,3-Dimethylallyl) 8 hydroxy-2-phenyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)_2C=CH-CH_2-$		2-Benzyl-3-(3,3-dimethylallyl)-8-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$		2-Benzyl-3-(3,3-dimethylallyl)-8-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)_3C=CH-CH_2-$	C_2H_5—	3-(3,3-Dimethylallyl)-2-ethyl-8-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine

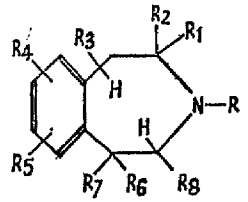
			Additional Examples
HO	$(CH_3)_2C=CH-CH_2-$	C_2H_5-	3-(3,3-Dimethylallyl)-2-ethyl-8-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine

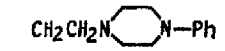
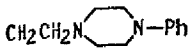
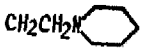
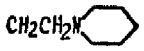
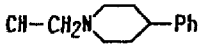
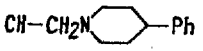
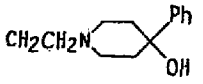
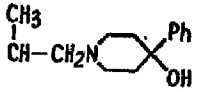


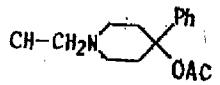
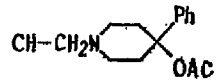
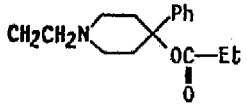
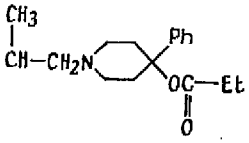
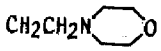
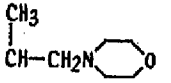
R^4	R	
CH_3O	$(CH_3)_2C=CH-CH_2-$	3-(3,3-Dimethylallyl(-8-methoxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	3-(3,3-Dimethylallyl)-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-Cyclopropylmethyl-8-methoxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-Cyclopropylmethyl-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$CH_2=CH-CH_2-$	3-Allyl-8-methoxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$CH_2=CH-CH_2-$	3-allyl-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		8-Methoxy-1-methyl-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		8-Hydroxy-1-methyl-3-phenethyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		3-(*p*-Aminophenethyl)-8-methoxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		3-(*p*-Aminophenethyl)-8-hydroxy-1-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O		8-Methoxy-1-methyl-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine
HO		8-Hydroxy-1-methyl-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine

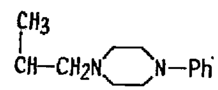
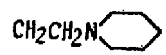
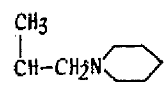
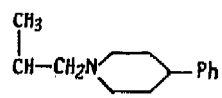
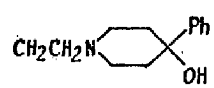
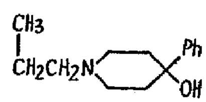
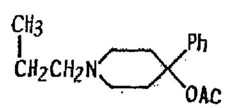
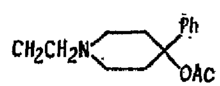


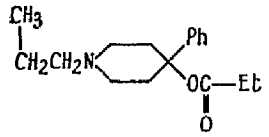
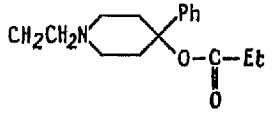
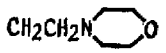
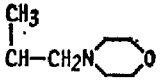
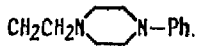
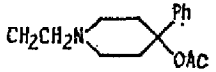
R^5	R	R^2	Additional Examples
CH_3O	$(CH_3)_2C=CH-CH_2-$	H	3-(3,3-Dimethylallyl)-6-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	H	3-(3,3-Dimethylallyl)-6-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine
CH_3O	$(CH_3)_2C=CH-CH_2-$	CH_3	3-(3,3-Dimethylallyl)-6-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine
HO	$(CH_3)_2C=CH-CH_2-$	CH_3	3-(3,3-Dimethylallyl)-6-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine



R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H

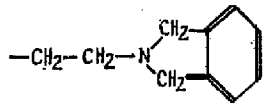
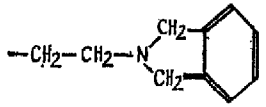
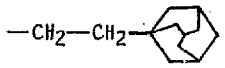
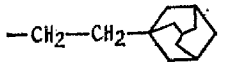
R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
$CH_2CH_2N(Me)_2$	H	H	H	HO	H	H	H	H
$CHCH_2N(Me)_2$ $\vert$ CH_3	H	H	H	HO	H	H	H	H
$CH_2CH_2N(Et)_2$	H	H	H	HO	H	H	H	H
$CHCH_2N(Et)_2$ $\vert$ CH_3	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	HO	H	H	H	H
	H	H	H	CH_3O	H	H	H	H

R	R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	R⁸
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H

R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
$CH_2CH_2N(Me)_2$	H	H	H	CH_3O	H	H	H	H
CH_3 | $CHCH_2N(Me)_2$	H	H	H	CH_3O	H	H	H	H
$CH_2CH_2N(Et)_2$	H	H	H	CH_3O	H	H	H	H
CH_3 | $CHCH_2N(Et)_2$	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	H	H	H	CH_3O	H	H	H	H
	CH_3	H	H	HO	H	H	H	H
	CH_3	H	H	CH_3O	H	H	H	H
	CH_3	H	H	HO	H	H	H	H

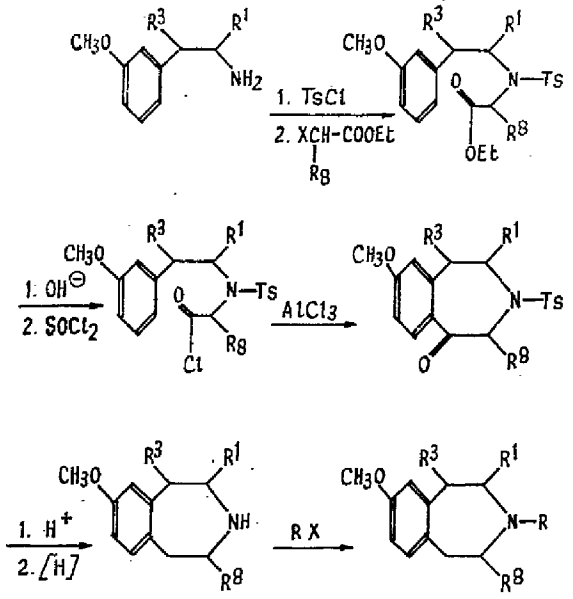
R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	CH_3	H	H	CH_3O	H	H	H	H
	CH_3	H	H	HO	H	H	H	H
	CH_3	H	H	CH_3O	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H
	H	H	H	HOC_3	H	H	H	H

R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	H	H	H	OH	H	H	H	H
	CH_3	H	H	OCH_3	H	H	H	H
	CH_3	H	H	OH	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	HO	H	H	H	H

R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H
	H	H	H	OCH_3	H	H	H	H
	H	H	H	OH	H	H	H	H

The following Reaction Scheme C illustrates a general method for preparing compounds of Formula I having alkyl substitution on the azepine ring.

Reaction Scheme C
ALKLY SUBSTITUTION ON THE AZEPINE RING



R^1, R^3 R^8 = H, lower alkyl
X = halogen
Ts Cl = toluenesulfonyl chloride

EXAMPLE 37

3-(p-Aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

A solution of *p*-toluenesulfonyl chloride (28.8 gm., 0.15 M) in benzene (100 ml.) was added dropwise to a solution of 2-(3-methoxyphenyl)-1-methylethylamine (23 gm., 0.139 M) and triethylamine (13 gm., 0.15 M) in benzene (200 ml.) during 30 minutes. The reaction was stirred at room temperature for 4 hours. The precipitated triethylamine hydrochloride was filtered off and the benzene solution was washed with hydrochloric acid (3N), water and saturated brine. The benzene solution was dried over magnesium sulfate. Evaporation of the solvent afforded N-toluene-*p*-sulfonyl-2-(3-methoxyphenyl)-1-methylethylamine as an oil. Wt=42 gm.

The crude sulfonamide (43 gm., 0.135 M) was dissolved in acetone (1100 ml.). Anhydrous potassium carbonate powder (135 gm.) was added and the reaction was stirred and refluxed. Ethylbromoacetate (33.7 gm., 0.202 M) was added in four equal portions at 30 minute intervals. After stirring and refluxing for 20 hours the salts were filtered from the cooled solution. Evaporation of the acetone gave an oily residue which consisted mainly of the alkylated amine. The ester function was hydrolysed by refluxing the oil with ethanol (95%, 900 ml.) and sodium hydroxide (10% aqueous, 270 ml.) for 6 hours. The ethanol was removed on the rotatory evaporator and the aqueous residue was diluted with water (1 l.) until a clear solution was obtained. The solution was washed with diethyl ether and then it was made acid with concentrated hydrochloric acid. The oily precipitate was extracted into ether and then the ether solution was washed with sodium bicarbonate solution. The bicarbonate solution was separated and acidified with concentrated hydrochloric acid and the precipitated acid was isolated in diethyl ether. The ether solution was dried over magnesium sulfate. Evaporation of the solvent afforded N-[2-(3-methoxyphenyl)-1-methyl] ethyl-N-toluene -*p*-sulfonyl glycine as a viscous oil which resisted crystallization. Wt=40.5 gm.

The crude acid (40 gm., 0.106 M) was refluxed in benzene solution (500 ml.) with thionyl chloride (25.3 gm., 0.212 M) for 9 hours. The excess thionyl chloride and solvent were removed on the rotatory evaporator. The crude acid chloride was dissolved in methylene dichloride (100 ml.) and added dropwise to a suspension of aluminum chloride (17.4 gm., 0.13 M) in methylene dichloride (300 ml.) which had been cooled to −65°C. The addition took 3 hours. The reaction was stirred at −65° for a further 7 hours and then it was stirred while warming to 15°C. during 12 hours.

The reaction mixture was poured onto ice (1500 gm.)/concentrated hydrochloric acid (75 ml.) and the mixture was stirred for 1.5 hours. The methylene chloride layer was separated and washed with water, sodium bicarbonate solution and saturated brine. Evaporation of the solvent afforded an oil. Wt=37 gm. The oil was purified by chromatography on silica gel. Elution of the column with acetone:benzene (1:40) afforded crude 3-(*p*-aminophenylethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine which was purified by crystallization from absolute methanol. Wt=11.4 gm. m.p. 119—121.5°.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92
Found: C, 63.77; H, 6.04; N, 3.61; S, 8.93

Further elution of the column afforded the 9-methoxy isomer which was crystallized from absolute methanol. Wt=1.5 gm. m.p. 127—128°.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92
Found: C, 63.41; H, 6.03; N, 3.65; S, 9.16

1-Hydroxy-7-methoxy-4-methyl-3-toluene-*p*-sulfonyl-1,2,4,5-tetrahydro-3H,3-benzazepine

Sodium borohydride (1 gm., 0.0264 M) was added during 5 minutes to a suspension of 7-methoxy-4-methyl-3-toluene-*p*-sulfonyl-1,2,4,5-tetrahydro-3H,3-benzazepin-1-one (7.5 g gm., 0.0208 M) in absolute ethanol (100 ml.) at room temperature. The mixture was warmed to 60° during 30 minutes and then the heat source was removed. After stirring for a further 3 hours at room temperature the reaction mixture was poured onto ice/concentrated hydrochloric acid (500 ml./25 ml.). The precipitate was extracted into chloroform. Evaporation of the chloroform afforded a viscous oil which, on trituration with diethyl ether afforded a solid. Wt=5.4 gm. m.p.=83—87°. The solid was crystallized from diethyl ether to give the pure title compound. m.p. 84—87°.

Anal. Calcd. for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88; S, 8.87
Found: C, 63.09; H, 6.40; N, 4.00; S, 9.11

8-Methoxy-2-methyl-3-toluene-*p*-sulfonyl-1,2-dihydro-3H,3-benzazepine

1 - Hydroxy - 7 - Methoxy - 4 - methyl - 3 - toluene - *p* - sulfonyl - 1,2,4,5 - tetrahydro - 3H,3 - benzazepine (7 gm., 0.0194 M) and *p*-toluene sulfonic acid (20 mg.) were dissolved in benzene (80 ml.) and the solution was refluxed for 1.5 hours. The solvent was condensed over a Soxhlet tube containing Linde Type 3A molecular sieves ($\frac{1}{16}$ inch). The solvent was evaporated and the residue was purified by chromatography on silica gel. Elution of the column with acetone:benzene (3:100) afforded an oil which solidified on trituration with diisopropyl ether to give the title compound. Wt=5.0 gm. m.p.=77—79°

Anal. Calcd. for $C_{19}H_{21}NO_3S$: C, 66.43; H, 6.16, N, 4.08; S, 9.34
Found: C, 66.26; H, 6.28; N, 3.93; S, 9.23

Further elution of the column afforded a solid which was crystallized from absolute methanol. Wt=0.38 gm. m.p.=177—182°

Found: C, 66.20; H, 6.38; N, 3.95; S, 9.52

8-Methoxy-2-methyl-3-toluene-*p*-sulfonyl-1,2,4-5-tetrahydro-3H,3-benzazepine

A solution of 8-methoxy-2-methyl-3-toluene-*p*-sulfonyl-1,2-dihydro-3H,3-benzazepine (4.7 gm., 0.0137 M) in acetic acid (50 ml.) was hydrogenated over 5% palladium-charcoal (0.4 gm.) in a Parr apparatus at an initial pressure of 37 psi. The adsorption of hydrogen was complete in 2.5 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was triturated with diisopropyl ethyl to give the title compound as a solid. Wt=4.3 gm. The solid was crystallized from absolute methanol. m.p.=86—89°.

Anal. Calcd. for $C_{19}H_{23}NO_3S$: C, 66.07; H, 6.71; N, 4.06; S, 9.28
Found: C, 66.10; H, 6.88; N, 3.97; S, 9.29

8-Methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

8 - Methoxy - 2 - methyl - 3 - toluene - *p* - sulfonyl - 1,2,4,5 - tetrahydro - 3H,3 - benzazepine (1 gm., 0.003 M) was suspended in liquid ammonia (35 ml.). Sodium (0.15 gm.) was added portionwise until the blue color persisted. After a further 15 minutes ammonium chloride (2 gm.) was added and the ammonia was allowed to evaporate. Water was added and the insolubles were extracted into diethyl ether. Evaporation of the ether afforded an oil. Wt=0.62 gm. The tile compound was

isolated as the hydrochloride salt and the salt was crystallized from iso-propanol. Wt=0.28 mg. m.p.=196—200°.

Anal. Calcd. for $C_{12}H_{17}NO$. HCl: C, 63.29; H, 7.97; Cl, 15.57; N, 6.15
Found: C, 63.34; H, 8.22; Cl, 15.33; N, 6.20

By following the procedure of example 26, 8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine is converted to the corresponding amide by *p*-nitrophenylacetic acid and dicyclohexyl-carbodiimide in tetrahydrofuran solution. Reduction of the amide in methanol solution over platinum oxide affords the corresponding amine, 3-(*p*-aminophenylacetyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine. The amino-amide is reduced by lithium aluminum hydride in tetrahydrofuran at reflux to give the compound, 3-(*p*-aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine.

EXAMPLE 38

3-(*p*-Aminophenethyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

By following the procedure of example 27, 3-(*p*-aminophenethyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine is demethylated by refluxing with 48% aqueous hydrobromic acid. The title compound is obtained from the hydrobromide salt by neutralizing with potassium carbonate solution.

EXAMPLE 39

3-(3-3-Dimethylallyl)-8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

By following the procedure of example 3, 8-methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine is treated with 1-chloro-3-methyl-2-butene and triethylamine in a solution of benzene and dimethylformamide to give the title compound.

EXAMPLE 40

3-(3,3-Dimethylallyl)-8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine

8-Methoxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine is treated with 48% aqueous hydrobromic acid at reflux. Evaporation of the excess acid affords the compound, 8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide. By following the procedure of example 4, 8-hydroxy-2-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrobromide is treated with triethylamine in dimethylformamide solution. The resulting amine is treated with 1-chloro-3-methyl-2-butene to give the title compound.

EXAMPLE 41

3-(p-Aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine methiodide

Iodomethane (1.5 gm., 0.0114 M) was added to a solution of 3-(p-aminophenethyl)-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine (3 gm., 0.0103 M) in acetone (40 ml.). The acetone was decanted from the gummy precipitate and the gum was triturated with ethyl alcohol (95%) to give the solid methiodide. The salt was recrystallized from water. Wt=0.8 gm. m.p.=236—239°.

Anal. Calcd. for $C_{20}H_{27}IN_2O$: C, 54.79; H, 6.21; I, 28.95; N, 6.39
Found: C, 54.64; H, 6.29; I, 29.13; N, 6.39.

PHARMACOLOGICAL ACTIVITY OF BENZAZEPINE COMPOUNDS

Compounds of the present invention have been evaluated in experimental animals for analgesic activity and ability to antagonize the action of strong narcotic analgesics. It has been possible through use of conventional testing methods in animals to demonstrate various degrees of these activities by one or several methods and routes of administration at dose levels which do not result in gross toxic manifestations. In addition, other pharmacological properties of representative compounds of this invention have been detected, such as antihistaminic and anticholinergic activity. Recognized indications of drug addiction typical of the opiates have not been observed following administration to the morphine dependent monkey indicatng a lack of addiction liabilty for these benzazepine compounds. Thus, results of pharmacological evaluations support the contention that the benzazepine compounds of the formulae disclosed in this application are of value as narcotic antagonist analgesics.

Results

Analgesic Activity

Table I provides a summary of the results obtained when representative compounds of this invention were tested for analgesic activity by the methods described. The narcotic antagonist analgesic pentazocine and the narcotic analgesics morphine and codeine are included for comparison. It is evident from this comparison that the

majority of compounds which exhibit significant activity at dose levels below those producing toxic manifestations, i.e., less than the highest non-symptomatic dose (HNSD), are effective primarily by the parenteral route. Exceptions are compounds SR654—66A, SR673—98A, SR727—52A, and SR701—77A which are active by the oral route. The predominance of parenteral efficacy is evident by both the hot plate method where the intraperitoneal route was used and by the writhing method with administration by the subcutaneous route. The most active compounds were SR673—98A, SR751—227A, SR673—50A, and SR753—850A. In addition, these compounds also exhibit the greatest separation between effective dose and toxic or lethal doses indicating a more favorable therapeutic index.

The most active compounds listed in Table I are comparable to codeine by the hot plate method of testing and are 6 to 10 times more active than pentazocine by the intraperitoneal route in this test. Compounds which exhibit activity by the oral route in the writhing test (SR654—66A, SR673—98A) are approximately twice as active as pentazocine.

The benzazepine compounds listed in Table II are examples showing narcotic antagonist activity determined by two methods. Inhibition of oxymorphine mydriasis in the mouse provided qualitative evidence of antagonist activity whereas inhibition of morphine analgesia in the rat permitted semiquantitative expression of antagonism. Narcotic antagonist activity was demonstrated for all of the benzazepine compounds in Table II by both the test methods. Compounds SR701—37A and SR673—98A appeared to be more potent antagonists than pentazocine whereas SR673—50A, SR727—52A and SR727—51A are about equipotent to pentazocine. No compound possessed activity approaching that of nalorphine, including the standard pentazocine. In addition to therapeutic application of these compounds as analgesics, narcotic antagonists have been of value in treatment of narcotic addiction.

For all benzazepine compounds listed, various degrees of similar toxic manifestations occurred with increasing dosage characteristics by depression, ataxia, reduced respiration, exophthalmose, salivation, lacrimation, vasodilation, cyanosis and mydriasis. Also common with all compounds was development of moderate to severe clonic convulsions and death of the animals was attributable to respiratory failure.

Antihistaminic and Anticholinergic Activity

Table III provides a summary of the relative antihistaminic and anticholinergic activity of benzazepine compounds as demonstrated through use of isolated segments of guinea pig ileum. It is apparent from these results that positive antihistaminic action can be elicited with the compounds listed in the table, the most potent of which, (SR673—98A) is approximately 25 time less active than the antihistaminic standard diphenhydramine. Weak anticholinergic activity relative to atropine was exhibited by these compounds.

TABLE I

Analgesic Activity of Benzazepine Compounds

Compound No.	Name	HNSD* mg/kg PO**	HNSD* mg/kg IP***	LD50 mg/kg PO	LD50 mg/kg IP	Hot Plate ED50 mg/kg PO	Hot Plate ED50 mg/kg IP	Writhing ED50 mg/kg PO	Writhing ED50 mg/kg SC****
SR753—850A	7-Methoxy-3-(p-acetamido-phenethyl)-1,2,4,5-tetra-hydro-3H,3-benzazepine hydrochloride	32	32	>1000	100	>32	9	>32	~7
SR673—50A	N-Phenethyl-7-methoxy-1,2,4,5 tetrahydro-3H,3-benzazepine hydrochloride	178	32	>1000	50	>178	12	>178	~11
SR654—66A	3-cyclopropylmethyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	56	18	477	52	37	12	49	>18
SR673-98A	3-(para-aminophenyl-ethyl)-7 methoxy 1,2,4,5 tetrahydro 3H,3-benzazepine dihydrochloride	100	18	445	52	85	17	45	~6
SR727—51A	3-Allyl-7-methoxy-1,2,4,5 tetrahydro 3H,3-benzazepine hydrochloride	178	56	>1000	60	>178	42	>178	>56
SR727—52A	7-Methoxy-3-(3-phenylallyl)-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	100	18	316	26	125	>18	120	>18
SR709—8A	3-Ethyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	125	30	1000	44	>125	15	>125	>32
SR701—77A	7-Methoxy-3-methyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	180	32	700	83	140	20	>180	>32
SR727—915A	7-Methoxy-3-n-propyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	316	32	686	50	>316	26	>316	>32

TABLE I (Continued)

Compound No.	Name	HNSD* mg/kg PO**	HNSD* mg/kg IP***	LD50 mg/kg PO	LD50 mg/kg IP	Hot Plate ED50 mg/kg PO	Hot Plate ED50 mg/kg IP	Writhing ED50 mg/kg PO	Writhing ED50 mg/kg SC****
SR673—64A	7-Hydroxy-3-phenylethyl-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	178	56	>1000	140	>178	26	>178	
SR701—87A	3-Allyl-7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	316	50	700	125	>316	35	>316	
SR751—227A	7-Methoxy-3-[2-(4-phenyl-1-piperazinyl)-ethyl]-1,2,4,5-tetrahydro-3H,3-benzazepine dihydrochloride	100	32	~300	~80	~80	~8	>100	
SR725—61A	3-(p-Aminophenethyl)7-hydroxy-1,2,4,5-tetrahydro-3H,3-benzazepine dihydrochloride	316	56	>1000	121	>315	37	>316	
SR727—42A	3-Cyclopentyl methyl-7-methoxy-1,2,4,5-tetrahydro-3H,3-benzazepine	178	56	784	75	>178	45	>178	
SR701—86	7-Hydroxy-3-(3-phenyl-allyl)-1,2,4,5-tetrahydro-3H,3-benzazepine	1000	300	>1000	—	>1000	230	210	
	Pentazocine	316	316	~800	>500	>316	100	70	
	Morphine	56	10	~800	250	14	2.5	3	
	Codeine	100	32	540	104	20	12	17	

* HNSD = Highest Non Symptomatic Dose
** PO = Per Os
*** IP = Intraperitoneal
**** SC = Subcutaneous

TABLE II

Narcotic Antagonist Activity of Benazepine Compounds

Compound No.	Name	Antagonism of Oxymorphone Mydriasis PO*	Antagonism of Oxymorphone Mydriasis IP**	Antagonism of Morphine Analgesia S.C.***
SR—701—37A	3-(3,3-dimethylallyl)-7-hydroxy-1,2,4,5 tetrahydro-3H,3-benzazepine hydrochloride	+	+	+++
SR—673—98A	3-(paraamino phenylethyl)-7-methoxy 1,2,3,5 tetrahydro-3H,3-benzazepine dihydrochloride	—	+	+ +
SR—673—50A	N-Phenethyl-7-methoxy-1,2,4,5 tetrahydro-3H,3-benzazepine hydrochloride	+	+	+
SR—727—52A	7-Methoxy-3-(3-phenyl-allyl)-1,2,4,5-tetrahydro-3H,3-benzazepine hydrochloride	+	+	+
SR—727—51A	3-Allyl-7-methoxy-1,2,4,5-tetrahydro 3H,3-benzazepine hydrochloride	+	+	+
	Pentazocine	+	+	+
	Morphine	—	—	—
	Codeine	—	—	—
	Nalorphine	+	+	Approximately 20—100 times more active than compounds listed above.

* PO = Per OS
** IP = Intraperitoneal
*** S.C. = Subcutaneous

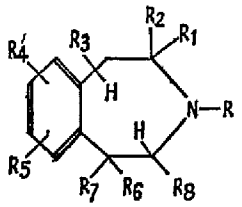
TABLE III

Antihistamine and Anticholinergic Activity of Benzazepine Compounds

Compound	Conc. for 50% block of Acetylcholine µg/20 ml	Conc. for 50% block of Histamine µg/20 ml
SR 701—37A	120	76
SR 727—43A	220	20
SR 701—89A	>1000	75
SR 730—243A	94	54
SR 673—98A	54	3
SR 725—61A	840	100
SR 654—66A	540	20
XR 673—50A	74	10
Atropine	0.0035	37
Diphenhydramine	3.3	0.12

WHAT WE CLAIM IS:—

1. A compound of the formula:



Formula I

or the pharmaceutically acceptable addition salts thereof, wherein R is H, lower alkyl, dialkylaminoalkyl; lower alkenyl containing 3—6 carbon atoms; aryl-C_3—C_6 alkenyl; cycloalkyl-alkyl; aryl-cycloalkyl-alkyl; propargyl; aryl-lower alkyl, the aryl group selected from phenyl, tolyl, nitrophenyl, aminophenyl, acylaminophenyl, methoxyphenyl, hydroxyphenyl, methylaminophenyl, ethylaminophenyl, or dimethylaminophenyl; a lower alkyl ester of hydroxyalkyl; a heterocyclic group, an alkyl group substituted by a heterocyclic ring (unsubstituted or substituted with one or more phenyl, hydroxyl or acyl groups), 2-phthalimidoethyl- (the phenyl moiety unsubstituted or substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-(2-isoindolinyl)-ethyl- (the phenyl moiety unsubstituted or substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-benzyl-1-piperazinyl]-ethyl- (the phenyl moiety unsubstituted or substituted in the *o*, *m*, or *p*-position with NH_2, OH, OCH_3); 2-(4-phenyl-1-piperazinyl)-ethyl- (the phenyl moiety unsubstituted or substituted in the *o*, *m*, *p*-position with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-(*o*-methylbenzyl)-1-piperazinyl]-ethyl- (the phenyl moiety unsubstituted or substituted in the *o*, *m*, or *p*-position with NH_2, OH, OCH_3, halogen, alkyl);

R^1 is hydrogen and R^2 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl, or R^1 and R^2 are lower alkyl;

R^3 is hydrogen or lower alkyl;

R^4 and R^5 are hydrogen, lower alkoxy, CH_3OCH_2O—, hydroxy, pyridine carboxylic acid ester of hydroxy group, amino, lower alkyl, halogen or nitro;
R^6 and R^7 are hydrogen, lower alkyl, phenyl or phenylalkyl;
R^8 is hydrogen, lower alkyl, phenyl or phenylalkyl; provided that when R^1, R^2, R^3, R^5, R^6, R^7 and R^8 are hydrogen and R is allyl, dialkylaminoalkyl or unsubstituted heterocyclylalkyl, R^4 is hydroxyl; provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 is other than hydrogen when R is either hydrogen, lower alkyl, allyl or phenyl-lower alkyl; and that neither R^4 nor R^5 is 6-chloro when R, R^1, R^2, R^3, R^6, R^7 and R^8 are hydrogen and provided that when R^4 and R^5 are methoxy R is not hydrogen or methyl.

2. A compound according to claim 1, in which R is 2-(1-adamantyl)-ethyl-(the adamantyl moiety being unsubstituted or subsituted with NH_2, OH, OCH_3, halogen or alkyl).

3. A compound according to Claim 1 in which R^4 and R^5 are hydroxy or lower alkoxy.

4. A compound according to Claim 1 in which R^4 and R^5 are hydroxy or lower alkoxy and R is hydrogen, lower alkyl or lower alkenyl.

5. A compound according to claim 1 in which one of R^4 and R^5 is hydrogen.

6. A compound according to claim 1 in which R^1 is methyl, R^2 through R^8 are hydrogen and R is hydrogen or *p*-aminophenethyl.

7. A compound according to claim 1 in which R^1 is methyl, R^4 is 7—OH, R^2, R^3, R^5, R^6, R^7 and R^8 are hydrogen and R is hydrogen or *p*-aminophenethyl.

8. A compound according to claim 1 in which R^1 is methyl, R^4 is 7—OCH_3, R^2, R^3, R^4, R^5, R^7 and R^8 are hydrogen and R is hydrogen or *p*-aminophenethyl.

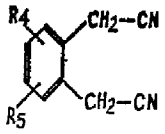
9. A compound according to claim 1 in which R^1 through R^8 are hydrogen and R is 2-(4-phenyl-1-piperazinyl)ethyl, 2-(4-phenyl-1-piperidinyl)ethyl, 3-phenylallyl, 3,3-dimethylallyl, cyclopropylmethyl, *p*-aminophenethyl or p-acetamidophenethyl.

10. A compound according to claim 1 in which R^4 is 7—OH, R^1, R^2, R^3, R^5, R^6, R^7 and R^8 are hydrogen and R is 2-(4-phenyl-1-piperazinyl)ethyl, 2-(4-phenyl-1-piperidinyl) ethyl, allyl, 3-phenylallyl, 3,3-dimethylallyl, cyclopropylmethyl, phenethyl, methyl, *p*-aminophenethyl or *p*-acetamidophenethyl.

11. A compound according to claim 1 in which R^4 is 7—OCH_3, R^1, R^2, R^3, R^5, R^6, R^7 and R^8 are hydrogen and R is 2-(4-phenyl-1-piperazinyl)ethyl, 2-(4-phenyl-1-piperidinyl)ethyl, 3-phenylallyl, 3,3-dimethylallyl, cyclopropylmethyl, phenethyl, methyl, *p*-aminophenethyl or *p*-acetamidophenethyl.

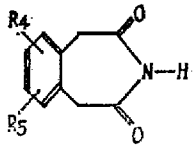
12. A process for preparing a compound of Formula I in which R through R^8 are as defined in claim 1, which comprises, when R is to be hydrogen in the compound of said Formula I,

a) treating a compound of the formula



Formula II

with a hydrogen halide in a polar solvent such as acetic acid, warming the resulting corresponding 2-amino-4-halobenzazepine derivative to provide a cyclic imide of the formula

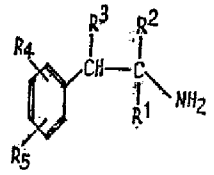


Formula III

and selectively reducing the carbonyl groups adjacent the imido group in the compound of Formula III;

b) hydrogenating a compound of said Formula II; or

c) when further any of the substituents R^1 through R^7 are to be lower alkyl, phenyl or phenyl lower alkyl, reacting an amine of the formula

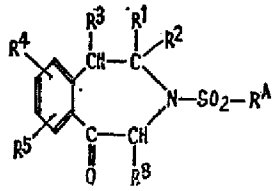


Formula IV

with a compound of the formula $R^A—SO_2X$ wherein R^A is an organic radical and X is halogen, reacting the corresponding sulfonamide thus obtained with an ester of the formula

Formula V

wherein *Alk* is a hydrocarbon group and X is halogen, hydrolyzing the resulting ester, treating the acid thus obtained with a halogenating agent such as thionyl chloride to provide the corresponding acid halide, adding the acid halide to a cold suspension of aluminum trihalide to provide a benzazepinone of the formula



Formula VI

selectively reducing the carbonyl group in the azepinone moiety of the compound of Formula VI and splitting off the radical $R^A—SO_2—$ therefrom; and, when R is to be other than hydrogen, reacting a compound of Formula I in which R is hydrogen with a reagent of the formula RX or R—C: OX wherein R is other than hydrogen and X is halogen, or with an aldehyde or ketone having at least three carbon atoms; and when a reagent of formula R—C: OX is used selectively reducing the carbonyl moiety to a methylene group.

13. The process of claim 12 wherein borane is employed to reduce the carbonyl groups of the compound of Formula III.

14. The process of claim 12 wherein the hydrogenation of the compound of Formula II is effected catalytically using Raney nickel catalyst.

15. The process of claim 12 wherein p-toluenesulfonyl chloride is employed as the compound of Formula $R^A—SO_2X$.

16. The process of claim 12 or 15 wherein ethylbromoacetate or an appropriately substituted derivative thereof is employed as the ester of Formula V.

17. The process of claim 12, 15 or 16 wherein the carbonyl group in the compound of Formula VI is selectively reduced with sodium borohydride.

18. The process of any of claims 12 to 17 wherein a reagent of Formula R—C: OX is reacted with a compound of Formula I wherein R is hydrogen and the carbonyl moiety in the product thereby obtained is reduced to a methylene group with lithium aluminum hydride.

19. The process of any of claims 12 to 17 wherein a compound of Formula I wherein R is hydrogen is reacted with an aldehyde or ketone having at least three carbon atoms and the double bond in the moiety attached to the nitrogen atom in the azepine ring of the product thereby obtained is reduced with sodium borohydride.

20. A pharmaceutical composition which comprises an excipient and as active ingredient a compound of Formula I in which R through R^8 are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

21. A compound of Formula I in which R through R^8 are as defined in Claim 1

substantially as hereinbefore described with particular reference to the Examples.

22. A process for preparing a compound of Formula I in which R through R^8 are as defined in Claim 1 substantially as hereinbefore described with particular reference to the Examples.

23. (−) - 3 - (*p* - amino - phenethyl) - 8 - methoxy - 2 - methyl - 1,2,4,5 - tetrahydro - 3H, 3 - benzazepine.

24. (+) - 3 - (*p* - amino - phenethyl) - 8 - methoxy - 2 - methyl - 1,2,4,5 - tetrahydro - 3H, 3 - benzazepine.

25. 7 - Methoxy - 3 - (p - acetamide - phenethyl) - 1,2,4,5 - tetrahydro - 3H,-3benzazepine hydrochloride.

26. 3 - (Para - amino phenyl - ethyl) - 7 - methoxy - 1,2,4,5 - tetrahydro - 3H,3 - benzazepine dihydrochloride.

27. 3 - (3,3 - dimethylallyl) - 7 - hydroxy - 1,2,4,5 - tetrahydro - 3H,3 - benzazepine hydrochloride.

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